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Total Syntheses of the Neuroregenerative Natural Products Vinaxanthone and Xanthofulvin and Biosynthetic Studies

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Total Syntheses of the Neuroregenerative Natural Products Vinaxanthone and Xanthofulvin and Biosynthetic Studies

by

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Dedication

This dissertation is dedicated to my family, M.G.A, A.A., and D.J.A. You have been with me through everything and have been my best cheering section, always.

Acknowledgements

The past several years have been quite an experience. I began this path when I was 20 years old in James Hendrickson's organic lectures at Brandeis, completely enamored with synthesis and determined to take my interest in organic chemistry as far as I could possibly go. The past ten years have taken me from industry in Boston, to Buffalo for an M.A., and finally here to UT Austin for my Ph.D. I arrived in Austin in 2007 as a 26 year old ready for graduate work, and excited for something I had wanted for several years. The past five years have been transformative. I've experienced tremendous failure, self-doubt in my abilities, the constant exhaustion and anxiety doctoral candidates face, and the feeling of incredible success and triumph over difficult research problems. I am now leaving my Ph.D. at 31 years old not only as a different scientist but also as a different person. There are several people who have made significant contributions to my development. I remember meeting Professor Dionicio Siegel for the first time at graduate recruitment in March 2007. Over the past five years I've learned many things from Dio. I've learned invaluable lessons at the bench - how to be a practitioner of making molecules, how to diagnose reactions and make them behave the way I want them to behave. Dio taught me that science isn't about papers or stereocenters or just knowing tricks to remove DMF from reactions and things like that.

I learned that science is a process of logically solving problems through asking good, creative questions, and that the answer to such a question is not the only importance. What is important is how one arrives at the answer and if the initial question was valid. Dio taught me that synthetic chemistry isn't just about making the most complex molecule one possibly can, or doing something new just because it's new. I learned that synthetic chemistry is an art of making molecules that are of importance and utility, and that a chemist uses creativity and logic to build structures to be used to solve problems. Dio showed me that just making a molecule, creative route or not, is just making a molecule. Making a molecule because it has macroscopic importance is what one should strive for. The molecule itself shouldn't be the only scientific question. I've learned to develop confidence in my hands and my mind, to link them together, and to harness my experience to succeed and to not dwell on failure and bad reactions. I will always look back fondly on chemistry in his laboratory and to discussions at the board and at our desks, scribbling ideas and going over references. It was a formative experience and one that propelled me to where I wanted to be at the end of my studies at UT Austin.

Throughout my time at UT Austin I've had the opportunity to meet with Professor Philip Magnus for both research and career advice. Every meeting was filled with great chemistry, and during my graduate work when I became stuck on a problem Professor Magnus's advice pointed me in the right direction and opened up reactions and chemistry I had not yet discovered on my own. Taking his class my first year was a fantastic experience and filled with real gems of synthesis that have influenced the types of problems I find interesting.

The first day in Professor Michael Krische's organometallics class was my first real introduction to organometallic chemistry. Upon hearing "You know how to count to eight, I'll show you how to count to 18," I had a feeling I would jump right in and enjoy learning new chemistry. It was one of the best courses I've ever taken and I looked forward to every lecture that first semester. Throughout my time at UT Austin, Professor Krische has given me great advice and was a valuable member of my candidacy and doctoral committees. Additionally, as a bright-eyed first year walking from Dio's office back to lab, Professor Krische stopped me in the hall and asked "Bramamine, how's it going?" It's the only time I've ever been called Bramamine, but he can call me that anytime.

Professor Adrian Keatinge-Clay has been a great committee member and a fantastic resource for understanding biosynthesis and biological chemistry. I've always enjoyed our conversations and am looking forward to working as a postdoctoral fellow in his laboratory.

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Total Syntheses of the Neuroregenerative Natural Products Vinaxanthone and Xanthofulvin and Biosynthetic Studies

Abram Joseph Axelrod, Ph.D.

The University of Texas at Austin, 2012

Supervisor: Dionicio R. Siegel

Total syntheses of the neuroregenerative natural products vinaxanthone and xanthofulvin have been accomplished. The synthetic routes to both molecules utilize a highly regioselective furan Diels-Alder cycloaddition - aromatization sequence to furnish the catechol fragment present in both natural products. The pentasubstituted catechol was elaborated to a vinylogous amide which was used twice in both syntheses, exploiting the pseudosymmetry found in vinaxanthone and xanthofulvin. This approach enabled the dimerization of 5,6-dehydropolivione forming vinaxanthone, lending significant evidence to a non-enzymatically driven formation of vinaxanthone in Nature. The total synthesis of vinaxanthone was accomplished in nine steps, the shortest synthesis to date, and an additional route was devised to access a set of analogs for biological study. The first total synthesis of xanthofulvin was accomplished in 18 steps and the convergent nature of the synthetic plan allows for analog synthesis. The sets of vinaxanthone and xanthofulvin analogs will be used to examine their inhibition of Semaphorin3A, a protein which inhibits neuronal regeneration, and is the biological target for both molecules.

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Chapter 1

Vinaxanthone and Xanthofulvin, Xanthones and Chromones, Semaphorin3A and Spinal Cord Injury.

The natural product vinaxanthone (**1**) was discovered in a *Penicillium vinaceum* (Gilman and Abbott NR6815) strain by scientists at Roche and the University of Tokyo as part of a screening program for phospholipase C inhibitors in 1991.[1] In 2003, Sumitomo Pharmaceuticals disclosed the isolation of vinaxanthone (**1**) along with a new molecule, xanthofulvin (**2**) (also known as SM-216289), from the fungal culture *Penicillium* sp. SPF-3059 as part of a broad research program for inhibitors of semaphorin3A (Sema3A), an inhibitor of spinal cord regeneration.[2] The *Penicillium vinaceum* fermentation produced 30 mg/L of vinaxanthone (**1**), and the *Penicillium* SPF-3059 fermentation produced 11 mg/L of vinaxanthone (**1**) and 21 mg/L of xanthofulvin (**2**). Currently there is no advance in the fermentative production of either molecule (Figure 1).

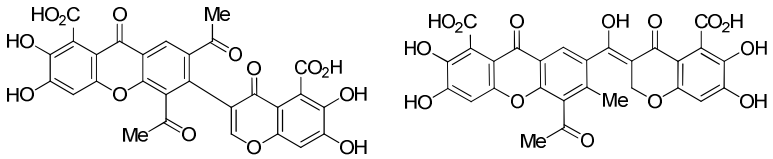

Figure 1. Structures of vinaxanthone (**1**) and xanthofulvin (**2**).

Structurally, these natural products possess both a xanthone and chromone core which is novel. Xanthones are produced from fungi, bacteria, and symbiotic composite

organisms – lichens. The structural motif, xanthone (*9H*-xanthen-9-one) is from the Greek word *xanthos*, meaning yellow (Figure 2).

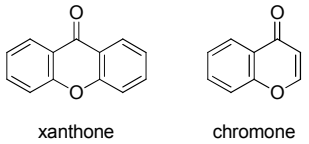

Figure 2. Xanthone and chromanone units.

This superfamily of compounds has found wide application in medicinal chemistry with broad biological activity and the number of xanthones known approximates 1,600 compounds.[3] The xanthone compounds can be divided into subclasses based on monomeric or dimeric structure and degrees of saturation. Vinaxanthone and xanthofulvin are considered to be heterodimers (Figure 3).

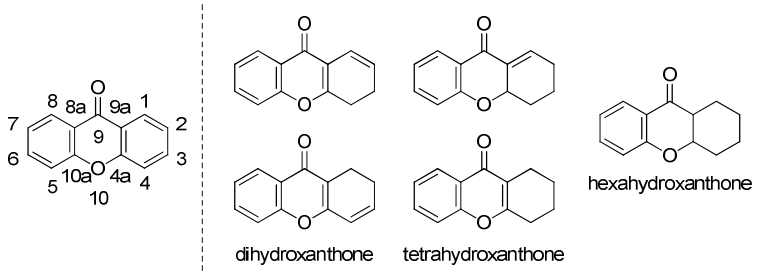

Figure 3. Xanthone subtypes.

There has been a long-standing interest in the biosynthesis and total synthesis of these molecules, and representative targets **3**-**7** are shown (Figure 4).[4-12]

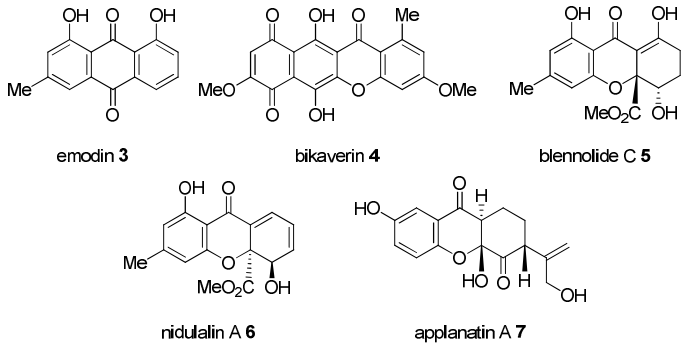

Figure 4. Xanthone molecules pursued in total synthesis.

In fungi, xanthones are synthesized in a head-to-tail assembly of eight acetate units into a polyacetate **8** which cyclizes to form an anthraquinone **9** which is oxidatively cleaved to **10** (Figure 5).[13-16]

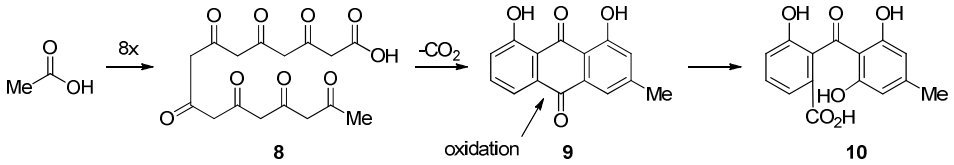

Figure 5. Xanthone biosynthesis in fungi.

Phenol **10** can then form xanthone **12** through a direct pathway or through a dihydroxanthone intermediate **11**. This sequence of events is organism dependant in fungi (Figure 6).

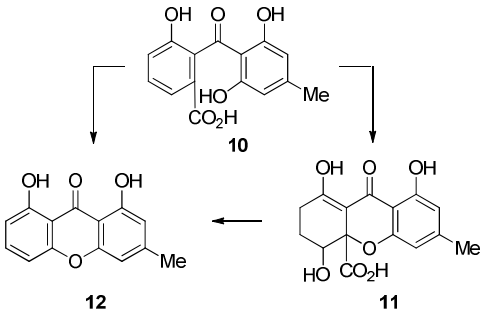

Figure 6. Divergent xanthone formation in fungi.

In plants, the biosynthesis of xanthones is from a mixed sequence of events. A shikimate pathway forms a hydroxybenzoic acid derivative which is coupled to a triacetate fragment, which forms the hybrid aromatic-polyacetate **13**.[17-23] Aromatization furnishes **14**, which can freely rotate around the aryl-ketone bond. This species can then undergo oxidative coupling to give xanthones **15** and **16**. It is known that this process can be catalyzed by xanthone cyclase (Figure 7).[24]

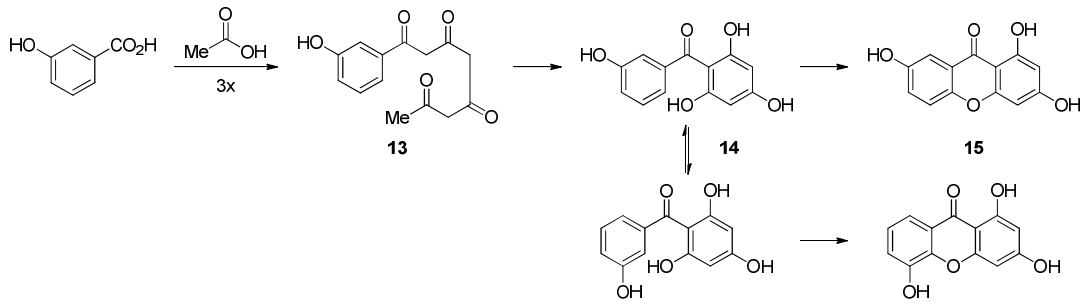

Figure 7. Xanthone biosynthesis in plants.

Diversity in xanthone synthesis can be also be illustrated in the oxidative modification of emodin **3**, where two different biosynthetic pathways are operative in a single fungal organism.[24] Through this pathway emodin **3** be oxidized to benzophenones **17** and **18** proceeding through a series of steps to blennolides A **19** and C **5** (Figure 8).

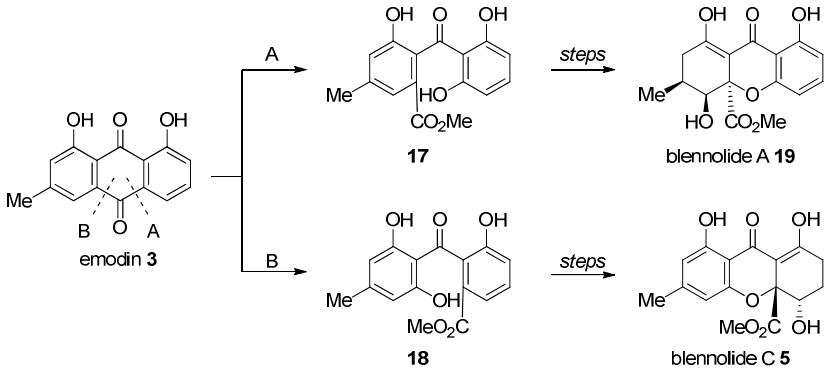

Figure 8. Emodin modification to blennolides A (**19**) and C (**5**).

Chromones are found in nature exhibiting various biological activity.[25-27] They have been shown to demonstrate monoamine oxidase (MAO) inhibition, anti-HIV activity, p38 MAP kinase inhibition, and anti-aromatase activity in the treatment of breast cancer.[28-31] Chromone (*4H*-1-benzopyran-4-one) and representative chromone natural products are shown **20-22** (Figure 9).

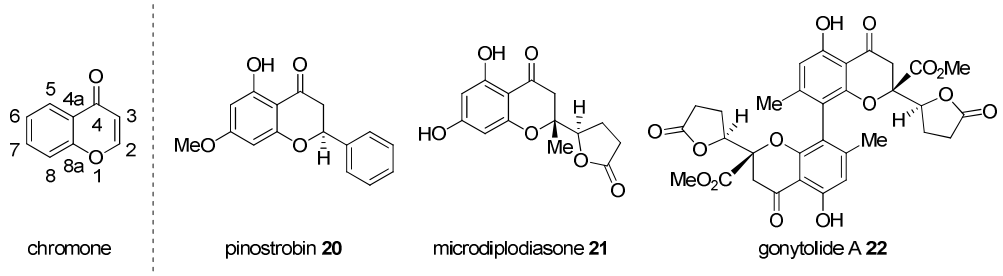

Figure 9. Chromone and chromone-based natural products.

Recent work on the biosynthesis of chromone compounds has been studied by both Abe and Zeeck. Abe found a plant type III polyketide synthase, pentaketide chromone synthase (PCS) producing pentaketide chromones (Figure 10).[32]

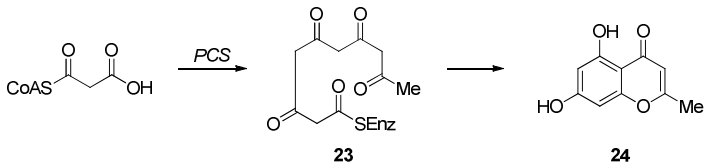

Figure 10. Pentaketide chromone synthase biosynthesis of chromones.

In this sequence five malonyl units are condensed to a pentaketide **23** which is cyclized to 5,7-dihydroxy-2-methylchromone **24**. Zeeck examined the biosynthesis of the chaetocyclinone polyketides isolated from an endosymbiotic fungus, *Chaetomium* sp. (Gö 100/2).[33] Through labeling studies a biosynthetic pathway was established and showed a similar heptaketide F-type folding to that found in fulvic acid (Figure 11).[34,35]

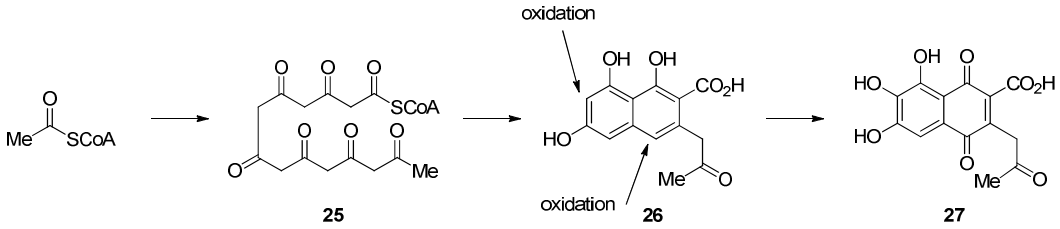

Figure 11. Biosynthetic pathway to chaetocyclinone B (**30**).

Polyketide synthase mediated folding of acetyl-CoA and six malonyl-CoA units forms heptaketide **25** which is cyclized to naphthol **26**. Oxidation furnished hydroxylated benzoquinone **27**, which is further oxidized and cyclized to chromone **29** (Figure 12).

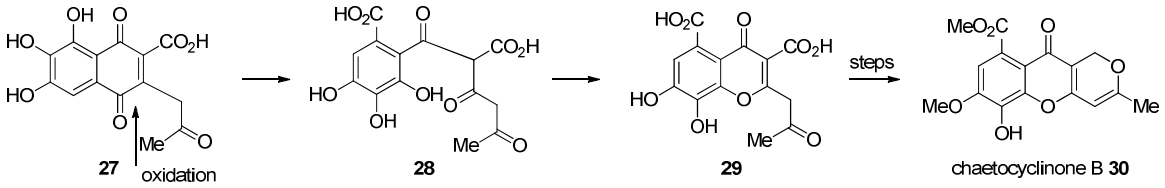

Figure 12. Oxidative pathway to chaetocyclinone B (**30**).

Representative fulvate-type natural products **30-33**, similar to chaetocyclinone B and fulvic acid are shown, and all are thought to be of similar biosynthetic origin (Figure 13).[36,37]

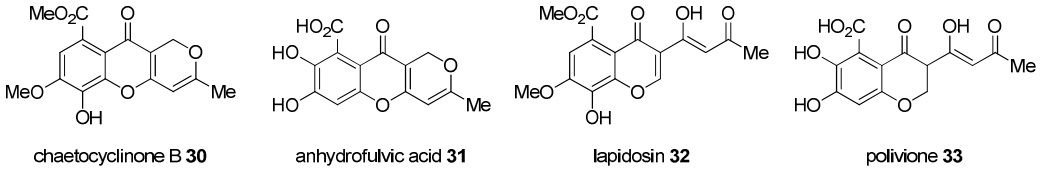

Figure 13. Fulvate-type natural products **30-33**.

While vinaxanthone (**1**) and xanthofulvin (**2**) are interesting from a structural and isolation standpoint, their biological profile is unique and is of significant interest. Vinaxanthone (**1**) and xanthofulvin (**2**) are potent inhibitors of Sema3A and have shown promise as small molecule therapeutics in the treatment of spinal cord injury (SCI).[38]

Semaphorins are a class of secreted or membrane-assiociated glycloproteins. There are more than 20 types of semaphorins categorized into eight classes on the basis of amino-acid sequence homology and structural features (Figure 14).[39,40]

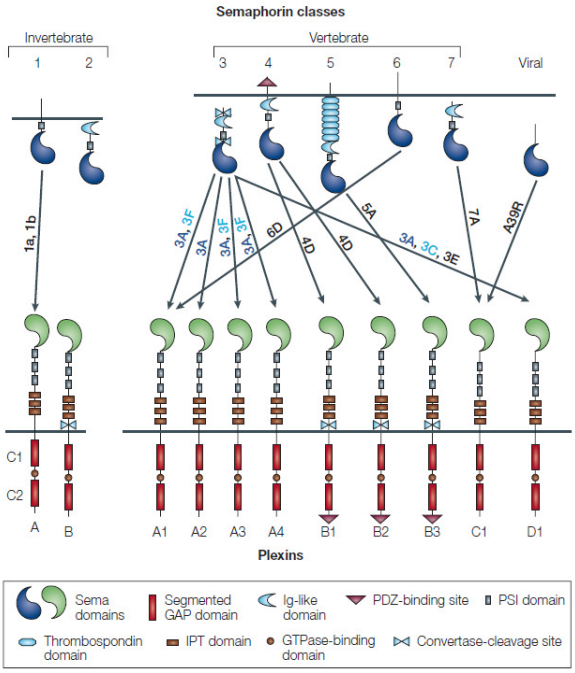

Figure 14. Semaphorin classes.[38]

All members of the semaphorins contain a conserved Sema domain, corresponding to approximately 400-500 amino acids.[41] Semaphorin3A is a secreted protein, structurally identified by Nikolov in 2003 as a 65 kDa soluble protein (Figure 15).[42]

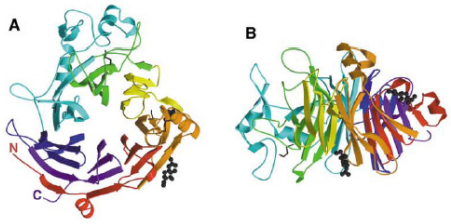

Figure 15. Top (A) and side (B) projections of Sema3A-65K secreted protein.[42]

Semaphorins act by forming a complex with their plexin receptors, which are divided into four classes among two types found in invertebrate species and nine in vertebrate species.[43] Semaphorin3A, however, is unique in that it uses a neuropilin as its direct receptor. Neuropilins are transmembrane glycoproteins involved in neuronal

development and survival. The functional sema3A-neuropilin complex then binds with plexins to affect biological activity.[43] Once this complex is formed the downstream effect is the collapse of growth cones. This can be shown (Figure 16).[44]

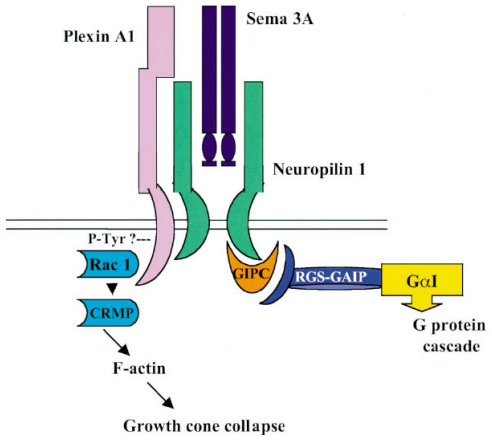

Figure 16. Semaphorin3A –Neuropilin1-Plexin complex inducing growth cone collapse.[44]

In spinal cord injury, a series of events occurs at the wound site. Scar tissue accumulates and production of sema3A is increased, inhibiting axonal regeneration.[45-47] Sema3A affects the actin cytoskeleton of neurons through microtubules in the cellular structure inducing growth cone collapse and chemorepulsion of new neurite outgrowth.[48-55] It is thought that inhibiting Sema3A and subsequently preventing the inhibition of new neurite formation would lead to enhanced neuronal development after traumatic spinal cord injury.

In 2006 a study on the effects of xanthofulvin (**2**), (also known as SM-216289), was published by Okano.[54] In this study it was found that xanthofulvin (**2**) inhibits the binding of Sema3A to neuropilin-1 (NP-1) by changing the steric structure involved in the association of the two proteins. The study examined, in detail, the *in vivo* effects of intra-spinal dosing with xanthofulvin (**2**) in complete transection model. The study found

that Sema3A accumulation was peaked 1-2 weeks post traumatic injury, corroborating a study which showed increased Sema3A mRNA at the lesion site in both transection and contusion injuries.[47] This study demonstrated *significant* functional and cognitive recovery *in vivo* over a 14 week dosing program, pronounced gain of function in rats.

The effects of dosing can be seen also in *in vitro* models.[54,55] It can be seen through increased dosing of xanthofulvin (**2**) in chick dorsal root ganglion cells that a direct correlation of new neurite outgrowth can be observed (Figure 17).[55]

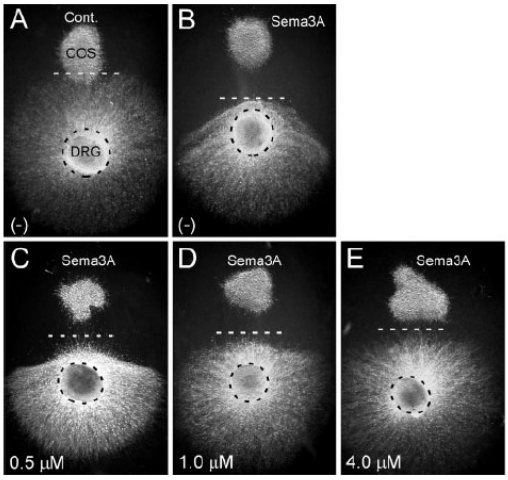

Figure 17. Increased chick dorsal root ganglion cell outgrowth with xanthofulvin (**2**).[55]

Similar findings were observed in the original isolation of xanthofulvin (**2**), with inhibition (IC_{50}) of Sema3A found at 0.09 μg/mL and at 0.1 09 μg/mL for vinaxanthone (**1**).[2] Importantly, the 2003 study showed no change in the cellular morphology after treatment with either natural product and no toxicity was observed at 1,000 times effective dosing.[2] The Okano study showed similarly outstanding results. The use of xanthofulvin (**2**) outperformed known inhibitors of Sema3A, lavendustin A **34** and olomoucine **35** (Figure 18).[54]

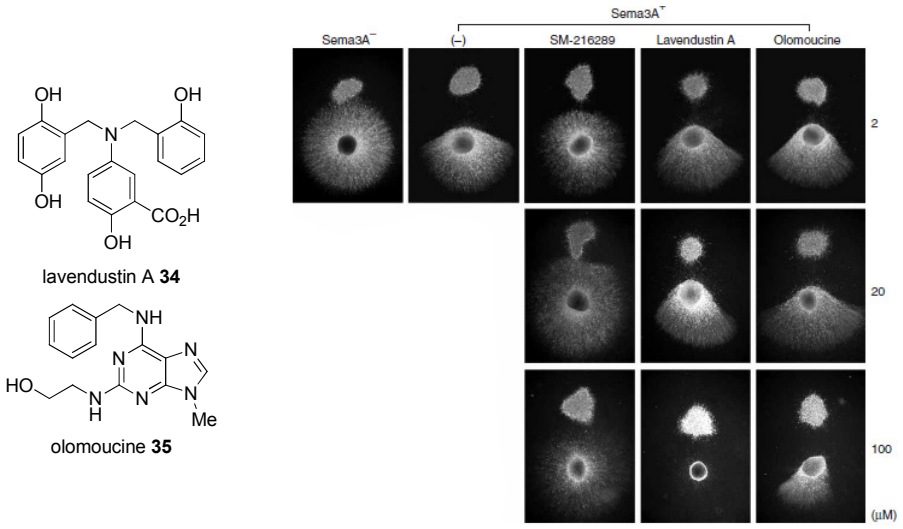

Figure 18. **I**nhibition of Sema3A in chick dorsal root ganglion cells structures of lavendustin A **34** and olomoucine **35**.[54]

The interesting structural features of these natural products coupled with their impressive biological profile and paucity make them outstanding candidates for total synthesis. There is currently no effective treatment for spinal cord injury, and while these two natural products might not become treatments, they have the potential to serve as outstanding tools for the study of neural regeneration in this context. Much is known about the process of Sema3A inhibition of neural regeneration, but a significant amount of progress can be made through the use of vinaxanthone (**1**) and xanthofulvin (**2**) to elucide more of the mechanisms involved in the anastomosis of neurons.

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Chapter 2

Synthesis of 5,6-Dehydropolivione and Total Synthesis of Vinaxanthone.

Prior to this work, the only total synthesis of vinaxanthone (**1**) was disclosed by Tatsuta in 2007 and is discussed here.[1] Retrosynthetically, vinaxanthone (**1**) can be simplified through a Diels-Alder/aromative oxidation sequence and protecting group transform to give enone **35** (Figure 1).

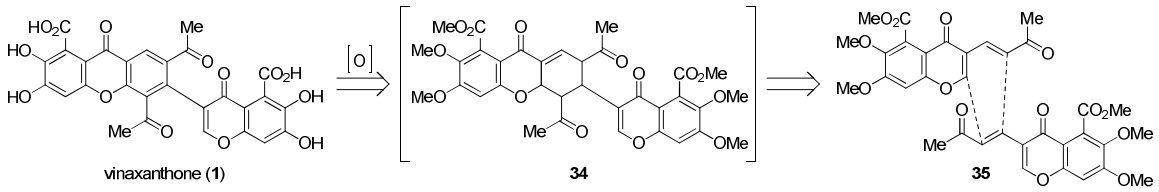


Figure 19. Vinaxanthone (**1**) retrosynthesis.

In the forward sense, bromination of vanillin **36** furnished aldehyde **37**, which was methylated to furnish dimethoxy-aldehyde **38**.[2] Dakin oxidation of the aldehyde and hydrolysis of the intermediate formate furnished phenol **39** (Figure 2).[3]

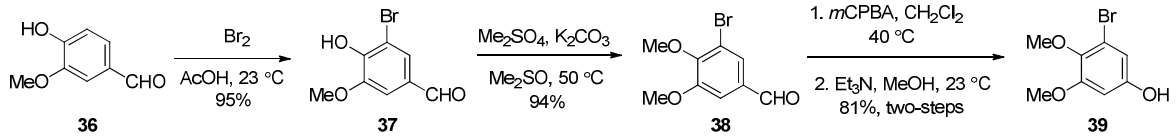


Figure 2. Synthesis of phenol **39**.

Conjugate addition of phenol **39** into acrylonitrile formed nitrile **40** which was hydrolyzed and cyclized under Friedel-Crafts conditions to afford chromanone **41**.[4] Subsequent ketalization with ethylene glycol and TsOH formed **42** (Figure 3).

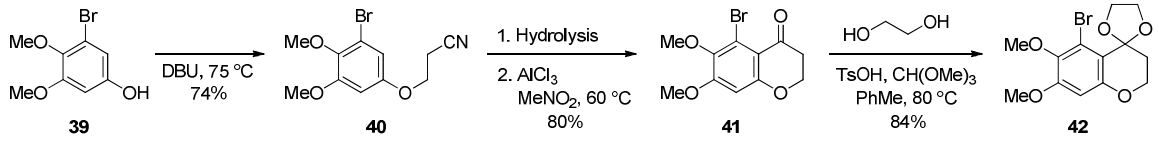


Figure 3. Synthesis of ketal **42**.

Ketal **42** was metallated with *n*-butyllithium and the resultant anion was trapped with methyl chloroformate to furnish, after hydrolysis of the ketal, methyl ester **43**. Vinyl iodide **44** was formed by treatment of **43** with iodine in hot dimethyl sulfoxide (Figure 4).

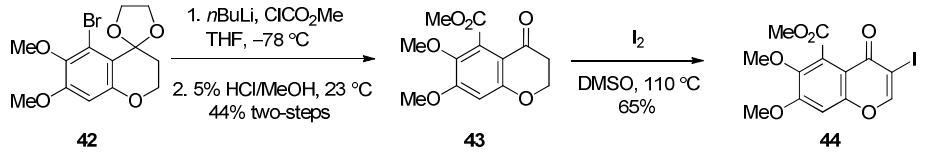


Figure 4. Synthesis of iodide **44**.

Iodide **44** was then coupled with methyl vinyl ketone to furnish enone **35**.[5] Dimerization in the presence of oxygen induced aromatization to form protected vinaxanthone **45**. In this transformation, Tatsuta asserts that this is a biomimetic dimerization and that in Nature, the Diels-Alder reaction proceeds to furnish vinaxanthone (**1**) (Figure 5).

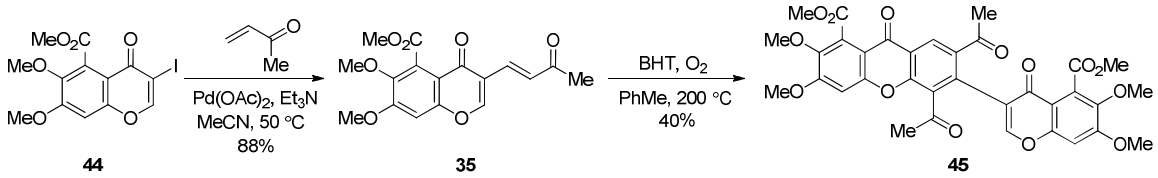


Figure 5. Synthesis of protected vinaxanthone **45**.

The last step was to deprotect all oxygen bound methyl groups and this was accomplished with $AlCl_3$ in refluxing toluene to furnish vinaxanthone (**1**) (Figure 6).

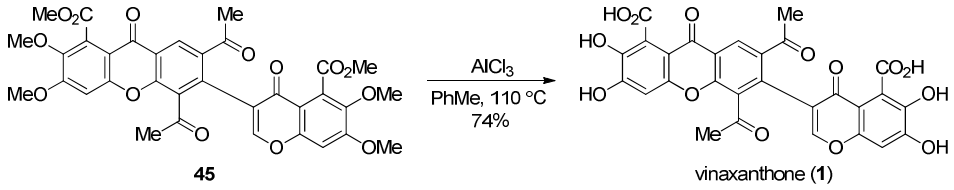


Figure 6. Deprotection of **45** to form vinaxanthone (**1**).

While this synthesis is short and relies on a clever dimerization strategy, the prospect of such a Diels-Alder cycloaddition occurring in Nature is of low likelihood.[6-8] An alternative biosynthetic hypothesis for the formation of vinaxanthone (**1**) was reported

by Wrigley and involved a dimerization of two C_{14} polyketides to form the C_{28} skeleton of vinaxanthone through an unknown mechanism (Figure 7).[9]

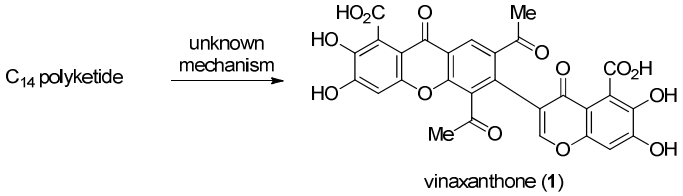


Figure 7. C_{14} polyketide dimerization to vinaxanthone (**1**).

A proposal the biosynthesis of structurally similar fungal metabolites was put forth by Zeeck.[10] In this proposal a heterodimerization of two C_{14} polyketides forms the C_{28} skeleton of chaetocyclinone C (**49**), similar in structure to that of vinaxanthone (**1**) (Figure 8).

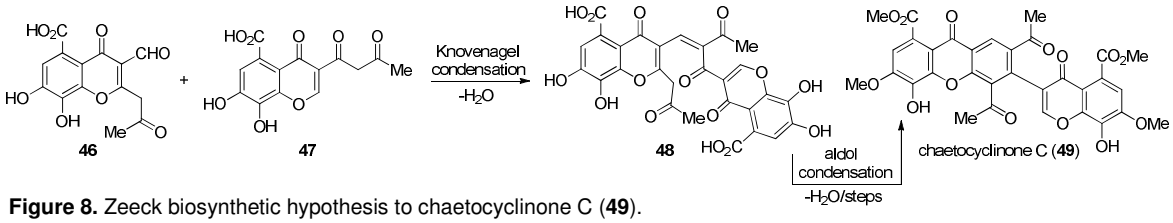


Figure 8. Zeeck biosynthetic hypothesis to chaetocyclinone C (**49**).

Interestingly there was no mention of the alternative reaction pathway where the speculated final aldol condensation occurs through the opposite alkene geometry in **50**. This alternative cyclization mode is shown below (Figure 9).

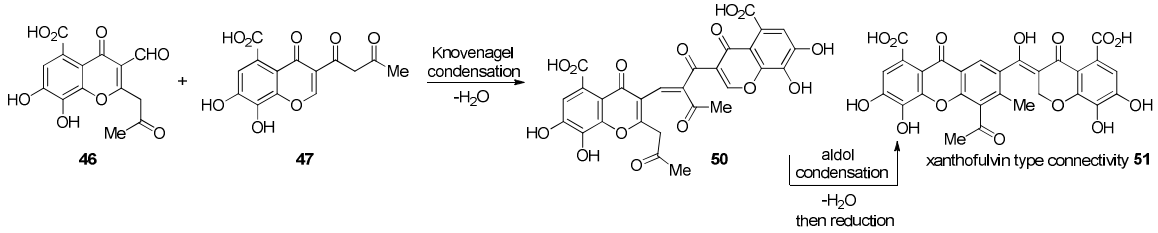


Figure 9. Zeeck biosynthetic hypothesis applied to xanthofulvin type connectivity **51**.

Analogously for vinaxanthone (**1**), Knovenagel condensation of keto-aldehyde **52** and 5,6-dehydropolivione (**53**) would furnish isomeric adducts **54** and **55**, differing only at

the enedione linkage.[11] Aldol condensation would form vinaxanthone (**1**) and dehydroxanthofulvin **62**, then undergoing reduction to form xanthofulvin (**2**) (Figure 10).

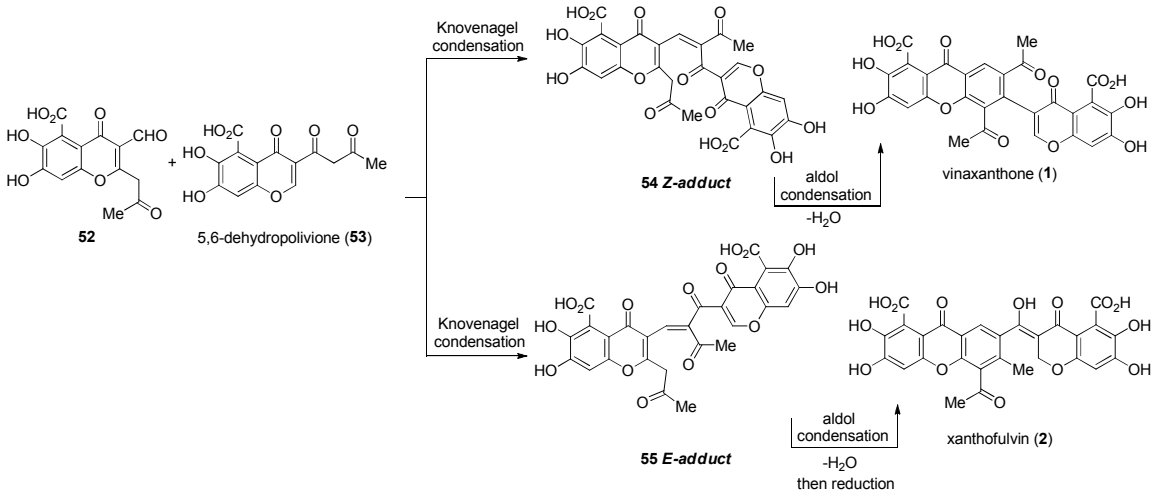


Figure 10. Zeeck biosynthetic hypothesis applied to vinaxanthone (**1**) and xanthofulvin (**2**).

Where both Tatsuta and Wrigley each proposed a homodimerization event of one monomer, Zeeck's proposal is a heterodimerization. However, upon further inspection of keto-aldehyde **52** it becomes clear that it is a rearranged form of 5,6-DHP (**53**). The following sequence illustrates the interconversion of 5,6-DHP (**53**) into **52** (Figure 11).[12]

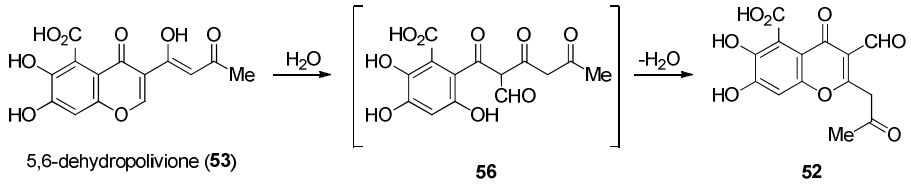


Figure 11. Conversion of 5,6-DHP (**54**) into keto-aldehyde **53**.

Addition of water into the chromanone of 5,6-DHP (**53**) followed by elimination gives rise to **56**, a highly reactive species which can cyclize in a 6-exo-dig fashion through attack of the proximal phenol onto the acetoacetate unit. After elimination of water, keto-

aldehyde **52** is formed. This heterodimerization pathway appears plausible but the existence of such a keto-aldehyde **56** might be fleeting due to its highly reactive nature.

In the previous isolation papers and total synthesis, vinaxanthone (**1**), xanthofulvin (**2**), and chaetocyclinone C (**49**) were isolated as axially achiral species. The barrier to rotation around the aryl-chromone bond in vinaxanthone (**1**) is estimated at ~20 kcal/mol, precluding stable axial chirality.[13] Additionally, because xanthofulvin (**2**) is co-isolated with vinaxanthone (**1**) it is highly suggestive of a non-enzymatically driven formation. After examining the three biosynthetic hypotheses for vinaxanthone (**1**) and xanthofulvin (**2**) a more complete mechanistic pathway can now be outlined (Figure 12).

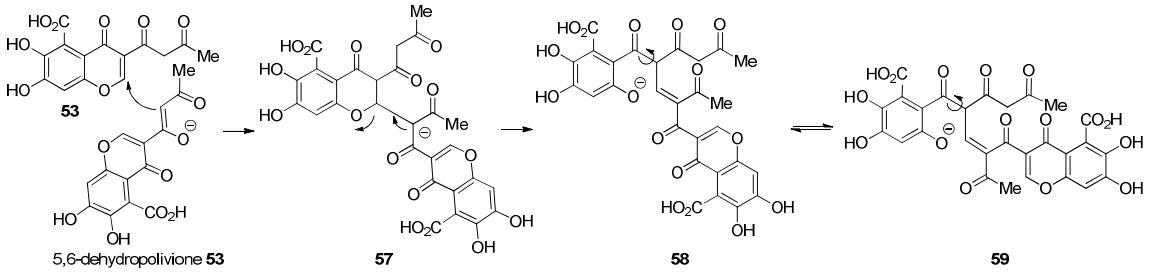


Figure 12. 5,6-DHP (**53**) dimerization pathway to vinaxanthone (**1**) and xanthofulvin (**2**).

Michael addition of 5,6-DHP (**53**) into another molecule of 5,6-DHP (**53**) is expected to furnish adduct **57**. Elimination forms enediones **58** and **59** which are in equilibrium with each other due to the highly delocalized nature of the tetracarbonyl system. Chromone condensation of **58** or **59**, both of which are in equilibrium, is expected to form **60** and **61** which are also in equilibrium with each other (Figure 13).

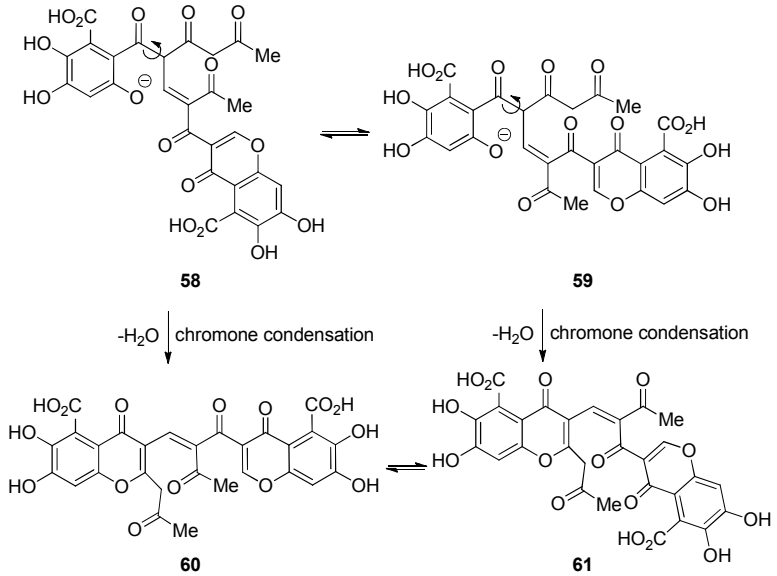


Figure 13. Chromone condensation to vinaxanthone and xanthofulvin precursors **61** and **62**.

Cyclization of **60** and **61** forms dehydroxanthofulvin **62** and vinaxanthone (**1**), respectively (Figure 14).

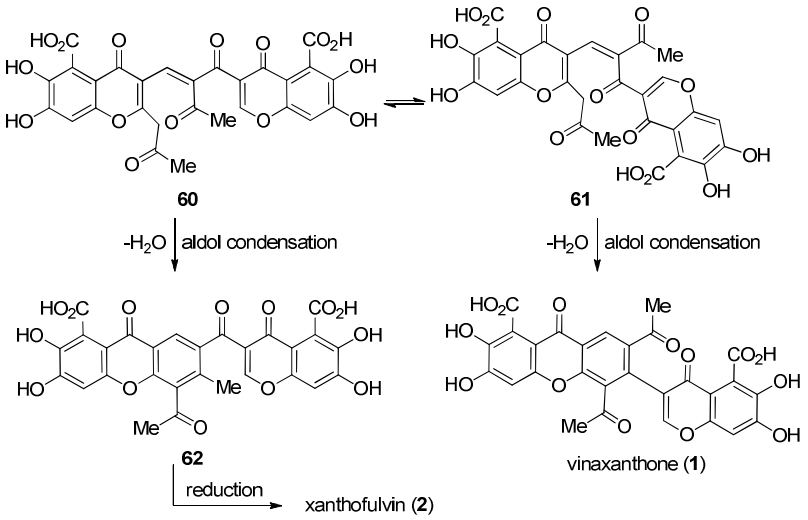


Figure 14. Vinaxanthone (**1**) and xanthofulvin (**2**) from cyclization precursors.

It is of note that the final cyclization step is speculated in the literature to be an aldol reaction. The pKa of the ketonic protons in **60** and **61** are low, estimated to be 3-4 and at physiologic pH it is likely that **60** and **61** exist in their trienol forms **63** and **64**. If both

molecules exist as their trienol forms then the likelihood of an aldol cyclization is low and the reaction can be more likely to occur through a 6π electrocyclization (Figure 15).[14,15]

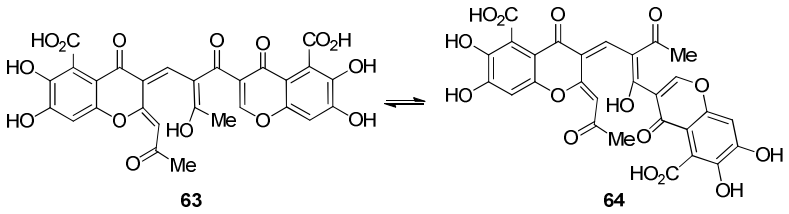


Figure 15. Trienol 6π electrocyclization substrates **63** and **64**.

Based upon our hypothesis for the non-enzymatic formation of vinaxanthone (**1**) in Nature, a concise synthesis for the putative monomer, 5,6-dehydropolivione (5,6-DHP) (**53**) was devised. Retrosynthetically, 5,6-DHP (**53**) can be simplified through a protecting group transform and deacetoacylation to pentasubstituted phenol **65** (Figure 16).

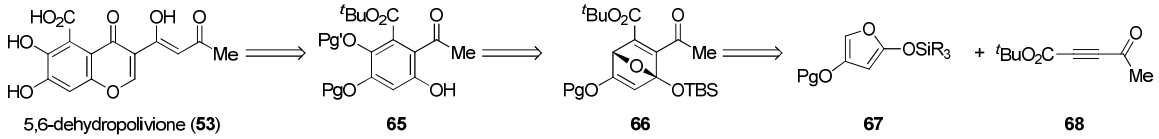
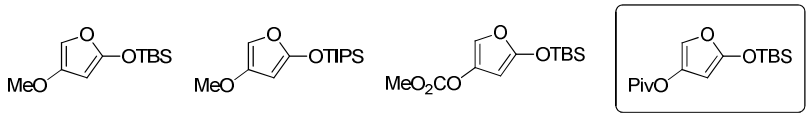


Figure 16. 5,6-DHP (**53**) retrosynthesis.

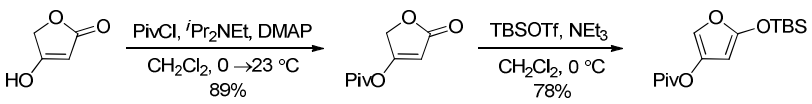
Phenol **65** is traced back to bicycle **66** which in the forward sense is the product of a furan Diels-Alder reaction between furan **67** and keto-ester **68**. Initial experiments into the reactivity of functionalized 2-siloxyfurans quickly demonstrated the requirement for an electron withdrawing substituent at the 4-position. Furans **69** - **72** were found to be unstable, decomposing rapidly and gave low yields of adducts in early studies (Figure 17).



69 **70** **71** **72**

Figure 17. Furans **69** - **72** examined in the key Diels-Alder reaction.

The use of the pivaloyl group, however, imparted not only enhanced stability but a significant improvement in yield of the Diels-Alder adduct. The synthesis of furan **72** is shown below and has been used to routinely deliver 100 g batches of product without the need for purification.[16] Acylation of tetronic acid **73** with pivaloyl chloride in the presence of catalytic 4-N,N-dimethylaminopyridine (DMAP) furnished crystalline, bench-stable pivaloyl tetronate **74** which was then silylated using *tert*-butyldimethylsilyl triflate in the presence of triethylamine to provide furan **72** (Figure 18).[17]



73 **74** **72**

Figure 18. Synthesis of furan **72**.

The synthesis of keto-ester **68** was accomplished in one of two ways. A short route (two-steps) employing a silver acetylide was initially used but was not scalable and required multiple reactions run in parallel to furnish sufficient quantities of keto-ester **68** (Figure 19).[18,19]

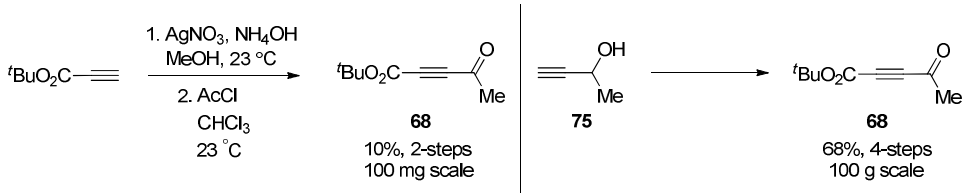


Figure 19. Synthesis of keto-ester **68**.

A second route was found to be eminently scalable (200 g scale) and despite being four steps long instead of two, was a more attractive option as the intermediates were also bench stable for storage. The latter route to keto-ester **68** is shown (Figure 20).[20]

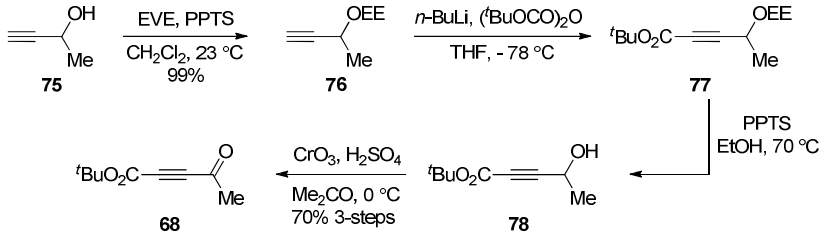


Figure 20. Scalable synthesis of keto-ester **69**.

Protection of commercially available 3-butyn-2-ol **75** as its ethoxyethyl ether **76**, followed by metallation and trapping with di-*tert*butyldicarbonate furnished **77** in nearly quantitative yield. After removal of the ethoxyethyl group and oxidation of the resultant carbinol **78**, keto-ester **68** was obtained as a pale yellow oil.

With significant quantities of both the diene and dienophile available the Diels-Alder reaction between furan **72** and keto-ester **68** was now investigated. While appearing straightforward, the Diels-Alder reaction between furans and unsymmetrical alkynoates is largely underreported.[21,22] In this case there are two possible regioisomeric outcomes of the cycloaddition (Figure 21).

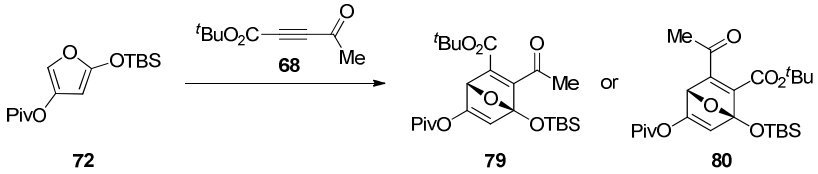


Figure 21. Diels-Alder cycloadducts **79** and **80**.

The desired adduct **79** arises from the most nucleophilic carbon of the furan attacking keto-ester **68** at the carbon distal to the ketone functionality, the most electrophilic

carbon. Mechanistically, this outcome is thought to be the most likely as the ketone is more electron withdrawing than the ester functionality and would exert a greater directing ability. The undesired adduct **80** would arise from the alternative mechanistic pathway where the ester functionality exerts a greater directing ability than the ketone (Figure 22).

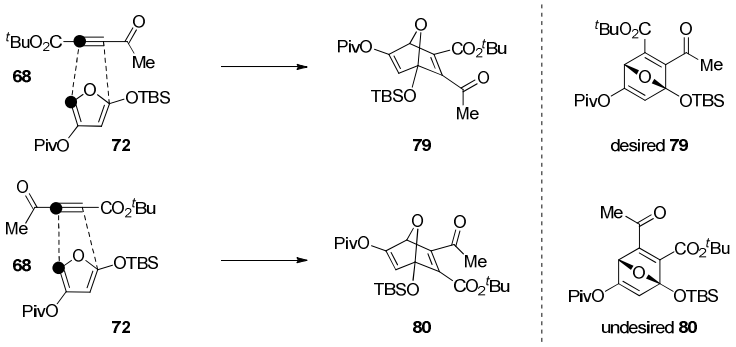


Figure 22. Diels-Alder adduct rationale.

It was anticipated that the ketone, being a stronger electron withdrawing substituent compared to the ester would influence the regioselection in concert with the polarization of the furan. Similar transformations are reported as intramolecular and are influenced by the use of a tether. A closely related transformation was reported by LeCoq using an unsymmetrical aldyhyde-ester alkyne, with regioselection governed by the ester and not the aldehyde.[23] This straightforward transformation now appeared to be less predictable that one would expect. Literature precedent exists for such transformations using symmetrical dienophiles such as DMAD.[24,25] Similar transformations are also reported as intramolecular and are influenced by the use of a tether.[26]

Admixture of a solution of furan **72** in THF and keto-ester **68** at 23 °C furnished, after concentration, a dark burgundy oil as a single regioisomeric product by NMR analysis. Both proton and carbon spectra showed an enol ether and bridgehead methine

found in the expected product. Bicycle **79** exhibited spectra consistent with an earlier variant of this system performed with a methyl carbonate instead of a pivaloyl ester which furnished the desired sense of regioselectivity, and was verified by crystallography. Bicycle **79** was then opened under acidic conditions, aromatizing to form phenol **81** with concomitant pivaloyl migration (Figure 23).

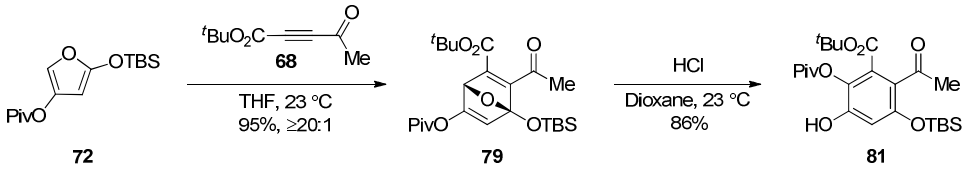


Figure 23. Diels-Alder adduct and aromatization to phenol **81**.

With large quantities of phenol **81** in hand the current object was to determine how to convert it into an acetoacetylated chromanone **82** (Figure 24).

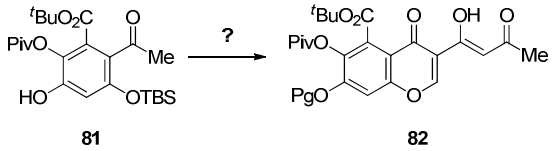


Figure 24. Phenol to protected 5,6-DHP **82**.

It was discovered quickly that the free phenol required protection as transformations on **81** were fraught with difficulty. The phenol was then protected as its methoxymethyl ether and the resulting pentasubstituted arene **83** was desilylated under the action of potassium methoxide to furnish hydroxyacetophenone **84** in good yield over this two-step sequence (Figure 25).

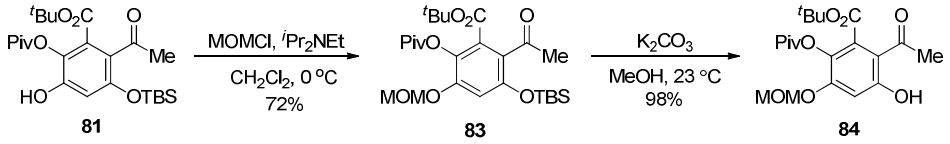


Figure 25. Synthesis of phenol **84**.

Early attempts to engage the *ortho*-hydroxy functionality of **84** in Baker-Venkataraman chemistry failed to furnish acetoacetylated products (Figure 26).[27,28]

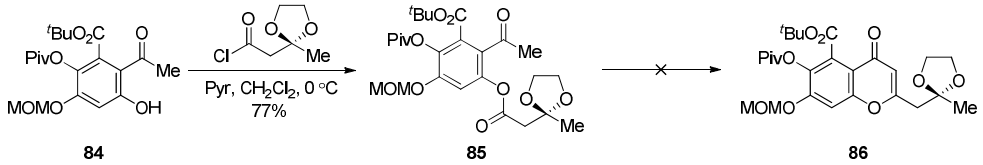


Figure 26. Attempted Baker-Venkataraman chromone formation.

The initial adduct **85** could be formed *in situ* or isolated, but the second step, the acyl transfer reaction never worked. Rigorous exclusion of water showed no benefit and only mixtures of recovered **85** or hydroxyacetophenone **84** were recovered. This can be attributed to the large steric bulk the *ortho-tert*-butyl ester imparts to the adjacent methyl ketone in **85**. Molecular models suggest enolization of the methyl ketone is impeded by steric compression and competitive hydrolysis of the phenolic ester becomes the dominant pathway. Interestingly, enol silyl ethers could be formed. Silylation was accomplished under the action of LDA and TMSCl, but the resulting bis-silyl compound did not productively engage any acyl electrophiles and this approach was not pursued further (Figure 27).

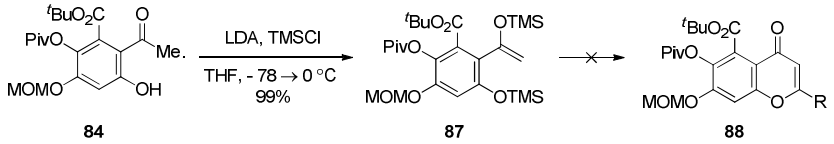


Figure 27. Attempted use of enolsilyl ether **87**.

Productive reactivity was observed in the piperidine-promoted aldol reaction of phenol **84** and isovaleradehyde.[29] The enone formed cyclizes to furnish **89** (Figure 28).

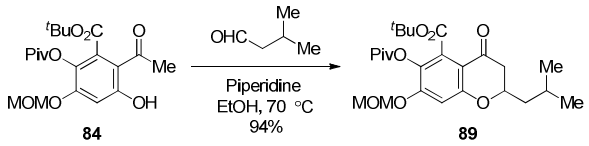


Figure 28. Aldol reaction and conjugate addition to furnish **89**.

This was not expanded with a different aldehyde as the product would require functionalization and desaturation to arrive at the desired subtarget.

In the course of course of these experiments the use of vinylogous amides became an attractive option for functionalizing phenol **84**. Enaminones **91** have been reported for the formation of halogenated and acylated chromones **92**, primarily in the context of pharmaceuticals, but not extensively in natural product total synthesis (Figure 29).[30,31]

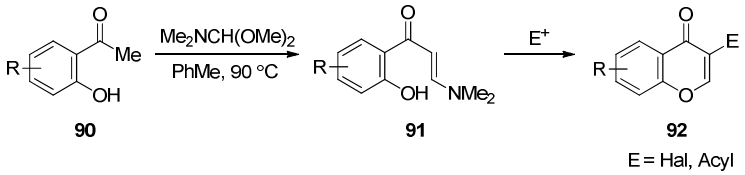


Figure 29. Application of the Gammill reaction to chromone **92**.

While this reaction has been demonstrated on unprotected *ortho*-hydroxy acetophenones, it was thought that at elevated temperatures the methoxide generated from the ionization of DMF-DMA would desilylate phenol **83** in the process of furnishing the corresponding vinylogous amide. In the event, phenol **83** was treated with excess DMF-DMA in hot toluene and gratifyingly vinylogous amide **93** was isolated in moderate yield (Figure 30).

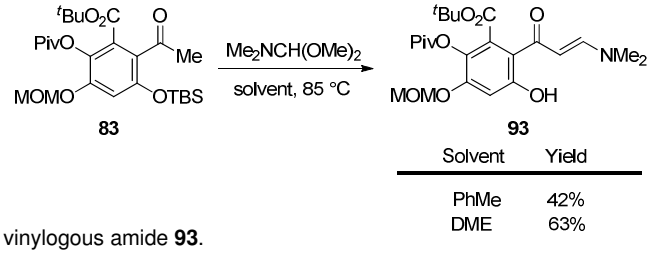


Figure 30. Formation of vinylogous amide **93**.

Toluene is the most utilized solvent for such transformations, however switching to dimethoxyethane greatly improved the yield of isolated product. Presumably, a polar solvent stabilizes the ionization of DMF-DMA and lowers the energy of the reactive intermediates.

With vinylogous amide **93** in hand, the next objective was to affect acetoacetylation. While acylation of enaminones are known through the use of activated acyl reagents, the following transformation has not been reported (Figure 31).[32]

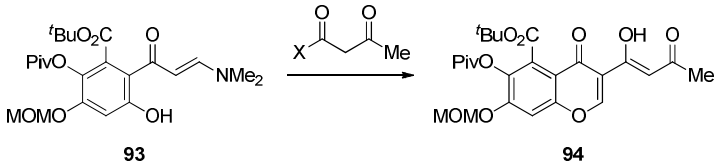


Figure 31. Direct acetoacetylation of vinylogous amide **93**.

The first reagent used to examine the feasibility of this reaction was the most obvious and the one that was expected to work on the first attempt. Diketene, however, did not furnish acetoacetylated product under several different reaction conditions. It was found that the use of acyl-Meldrum's acid **95** smoothly affected direct acetoacetylation of vinylogous amide **93** in good yield for this transformation (Figure 32).[33]

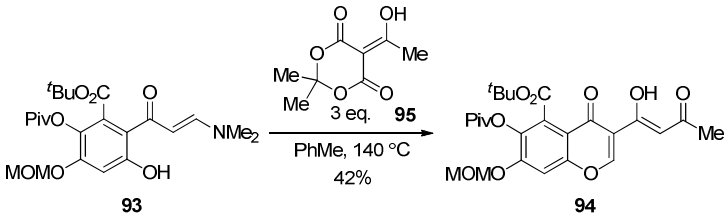


Figure 32. Direct acetoacetylation of vinylogous amide **94** with acyl Meldrum's acid **96**.

The major byproducts from the reaction were chromanone **96** arising from competitive cyclization of the enamenone **93** and dehydroacetic acid **97** resulting from the Diels-Alder cycloaddition of *in-situ* formed acyl-ketene from decomposition of **95** (Figure 33).

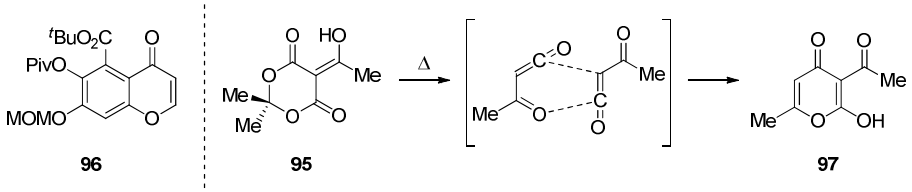


Figure 33. Byproduct formation during acetoacetylation.

With protected 5,6-DHP **94** in hand, the deprotection was accomplished through the use of boron trichloride and furnished 5,6-DHP (**53**) in good yield (Figure 34).[34]

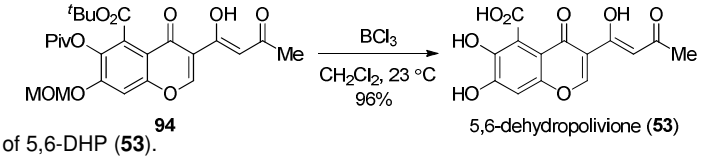


Figure 34. Synthesis of 5,6-DHP (**53**).

The key biomimetic dimerization sequence was now explored. Heating 5,6-DHP (**53**) in deionized water lead to dimerization to form vinaxanthone (**1**) (Figure 35).

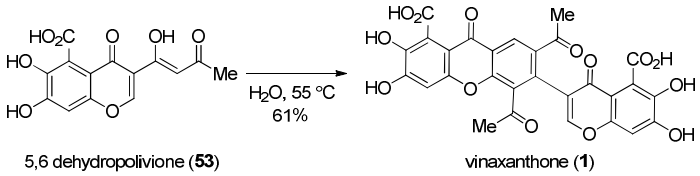


Figure 35. Dimerization of 5,6-DHP (**53**) to form vinaxanthone (**1**).

Further, no evidence of xanthofulvin was detected from the reaction. Examining the mechanistic proposal suggests two explanations for the exclusive formation of the vinaxanthone connectivity. Trienol **98** can undergo 6π-electrocyclization to give **99** which can engage in a reversible intramolecular conjugate addition furnishing **100**. This reversible conjugate addition suppresses the dehydration to form **101** (Figure 36).

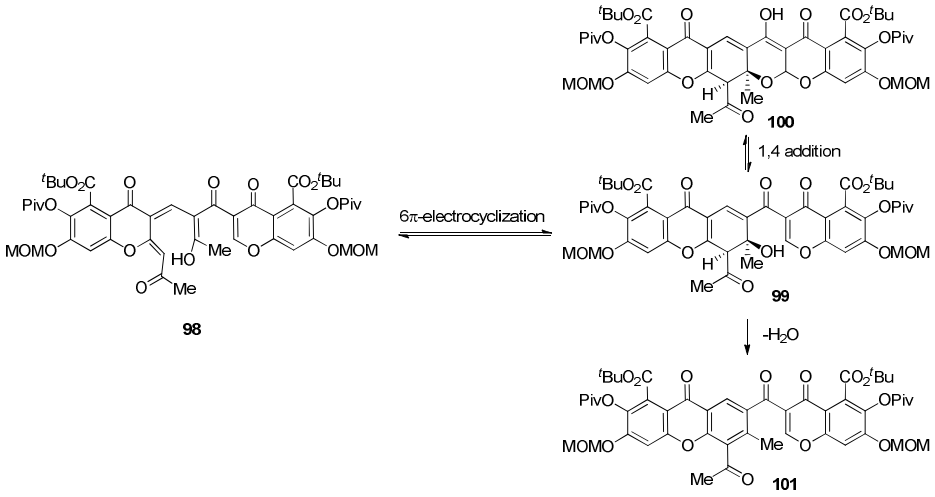


Figure 36. Mechanistic rationale for the exclusive formation of vinaxanthone (**1**).

The second feature which accounts for the formation of vinaxanthone over xanthofulvin is the aromaticity-assisted hydrogen bonding found in **103**.[35-37] Through resonance, the chromanyl unit in **102** can aromatize, stabilizing the transition state for the 6π-electrocyclization, in the cascade forming vinaxanthone (**1**) (Figure 37).

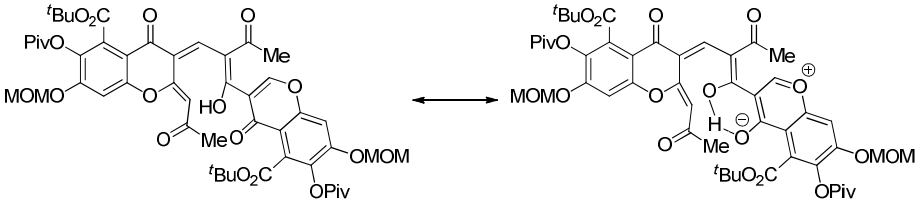


Figure 37. Aromaticity assisted hydrogen bonding in **103**.

Having established a bioinspired synthesis of vinaxanthone (**1**), the next focus was to develop a laboratory preparation for larger quantities of vinaxanthone and one amenable to the synthesis of analogs and probes used in target identification studies. Acyl ketone **94** was found to be very reactive, and a system containing only a Michael acceptor would attenuate background reactivity. It had been found that an alkynone **104** could function as a surrogate for the acetoacetate functionality on **94** (Figure 38).

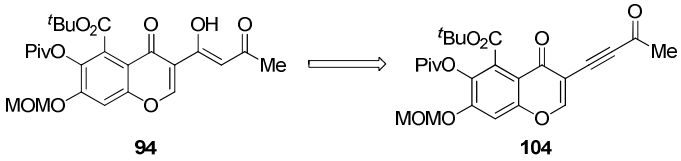


Figure 38. Ynone **104** as a surrogate for acylketone **94**.

The route to ynone **104** was pursued as follows. Iodination of enamenone **93** could be accomplished by treatment of the vinylogous amide with iodine in chloroform at 23 °C to furnish iodochromanone **105** as a white solid (Figure 39).[30]

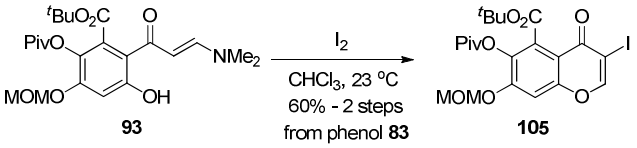


Figure 39. Synthesis of iodochromanone **105**.

With significant quantities (20-30g) of this compound in hand the next transformation required was a Sonogashira coupling of iodochromanone **105** with 3-butyn-2-ol **75**.[38-40] Initial conditions furnished low yields (35-40%) of coupled product **106** with recovered iodochromanone **105** suggesting either no oxidative addition occurred in to the carbon-iodine bond *or* decomposition of the active catalyst was occurring. It was found through degassing the THF that the yield could be augmented and was scalable to 3 to 5 grams (Figure 40).

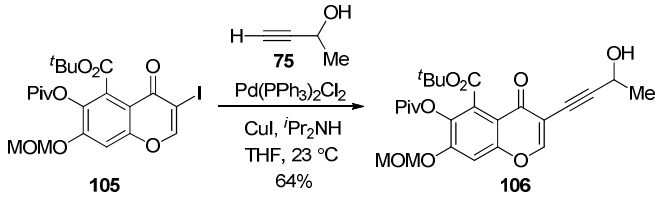


Figure 40. Sonogashira reaction of **105** to form carbinol **106**.

Oxidation of **106** proved to be non-trivial. Oxidation methods including Swern, tetra *n*-propyl ammonium perruthenate (TPAP), or Dess-Martin reagent did not furnish product and destroyed the substrate. Manganese dioxide oxidation was found to be batch dependent. Corey-Schmidt oxidation worked consistently to smoothly oxidize carbinol **106** to ynone **104** in reliable yield and on multi-gram scale (Figure 41).[41]

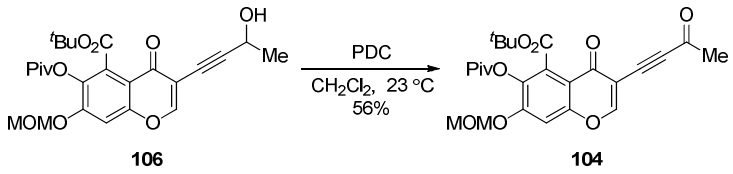


Figure 41. PDC oxidation of **106** to furnish ynone **104**.

It was thought that a cascade sequence between ynone **104** and protected 5,6-DHP **93** would furnish vinaxanthone (**1**) (Figure 42).

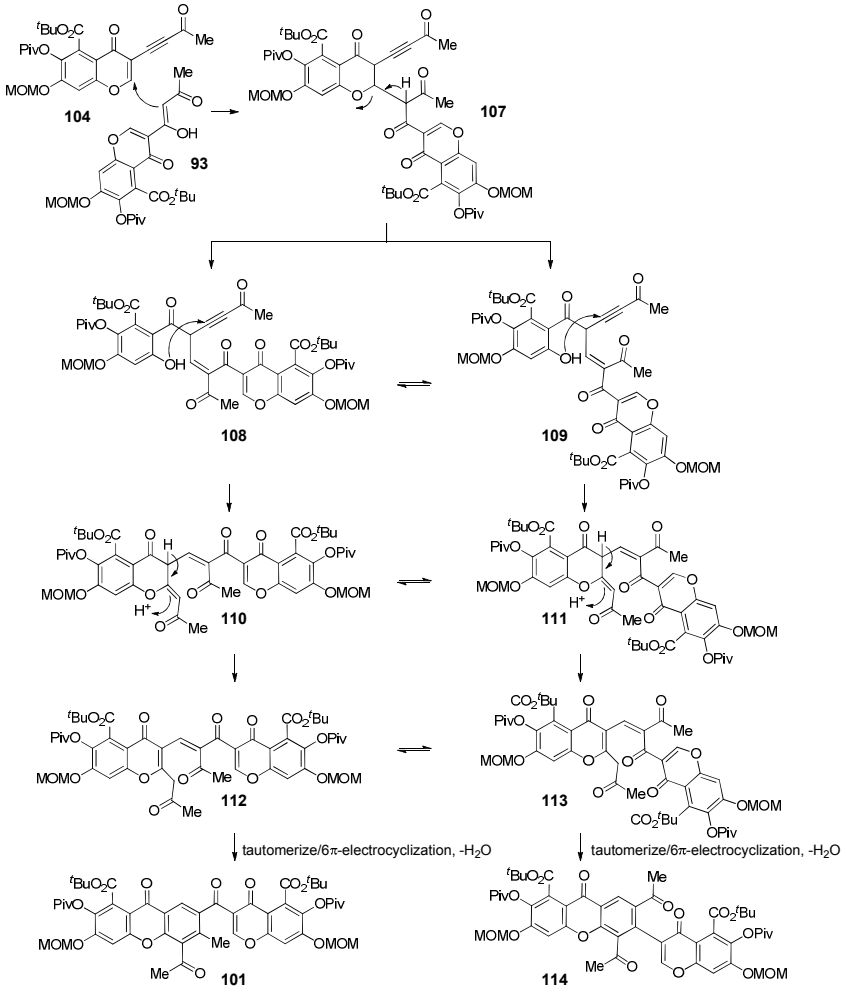


Figure 42. Proposed cascade of ynone **104** and acyl ketone **93** to furnish protected vinaxanthone **114**.

Michael addition of **93** into ynone **104** would form adduct **107** which could eliminate to alkenes **108** and **109** which are interconvertible. In each conjugate addition of the free phenol onto the alkene would furnish **110** and **111** which are both interconvertible. Compounds **112** and **113** are expected to participate in 6π-electrocyclizations to form protected vinaxanthone **114** and protected

dehydoxanthofuvlin **101**, although based upon the postulated reactivity for a xanthofulvin isomer to equilibrate back to **99**, it was not expected to be detected in the reaction. Exposure of a 1:1 ratio of protected 5,6-DHP **93** and ynone **104** to Et_3N in acetonitrile at 23 °C did not furnish protected vinaxanthone **114** (Figure 43).

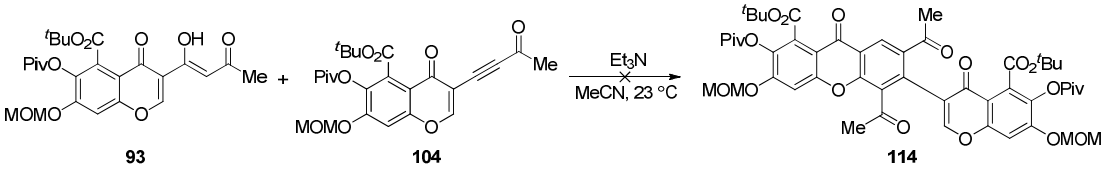


Figure 43. Reaction of protected 5,6-DHP **93** and ynone **104**.

It was found, however, in control experiments that ynone **104** alone dimerized under the same reaction conditions affording protected vinaxanthone **114** (Figure 44).

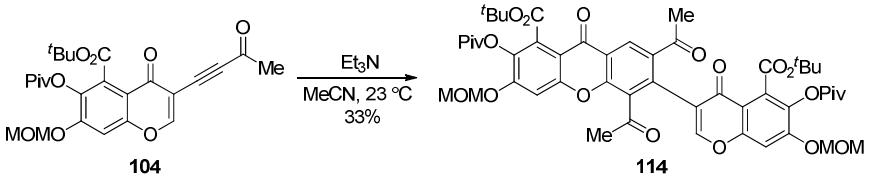
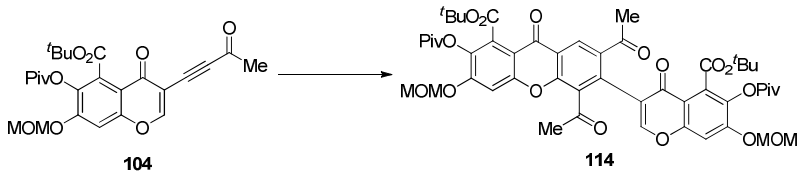


Figure 44. Homodimerization of ynone **104** to furnish protected vinaxanthone **114**.

This result is important, suggesting that an unknown variable is involved in the transformation of ynone **104** into protected vinaxanthone **114**. It was found in subsequent experiments that water is required for this transformation to work. Careful investigation in to the role of water is shown (Table 1).



Entry	Base	H_2O	Solvent	Temperature (°C)	Time (h)	Yield
1.	Et_3N	0 eq.	MeCN (dry)	23	16	0%
2.	Et_3N	0.1 eq.	MeCN (dry)	23	16	65%
3.	Et_3N	0.5 eq.	MeCN (dry)	23	16	87%
4.	Et_3N	1.0 eq.	MeCN (dry)	23	16	67%
5.	Et_3N	2.0 eq.	MeCN (dry)	23	16	59%
6.	Et_3N	0 eq.	MeCN (wet)	23	16	54%

Table 1. Optimization data for homodimerization to protected vinaxanthone **114**.

Based upon the optimization data, a proposed mechanism for the hydration of ynone **104** to keto-aldehyde **118** is shown below (Figure 45).

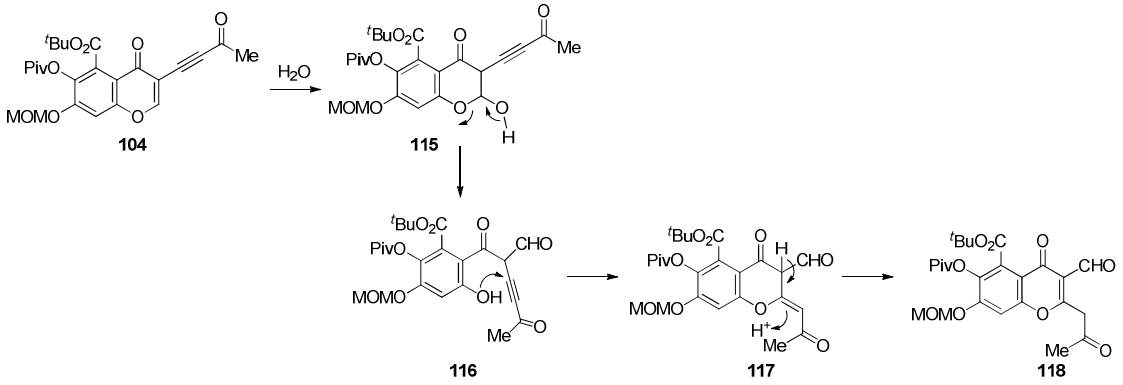


Figure 45. Proposed hydration-isomerization mechanism of ynone **104** to keto-aldehyde **118**.

Addition of water into the chromone of **104** should furnish hemiacetal **115** which should eliminate to form aldehyde **116**. Addition of the proximal phenol into the alkynone should furnish, after isomerization, keto-aldehyde **118**. Proof of concept for keto-aldehyde **118** being a competent species in the proposed reaction sequence was obtained by converting ynone **104** to keto-aldehyde **118** through addition of 1000 equivalents of H_2O to ynone **104** (Figure 46).

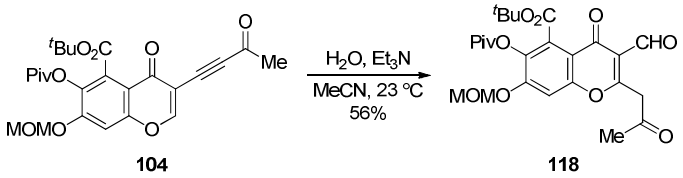


Figure 46. Isolation of keto-aldehyde **104** through hydration of ynone **118**.

Finally, treatment of isolated keto-aldehyde **104** and ynone **118** with Et_3N in MeCN furnished protected vinaxanthone **114** in comparable yield to the *in-situ* conversion of the ynone **104** monomer to keto-aldehyde **118** (Figure 47).

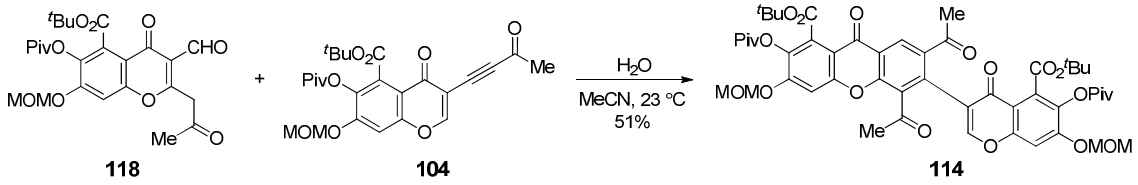


Figure 47. Heterodimerization of keto-aldehyde **118** and ynone **104** to furnish protected vinaxanthone **114**.

Two possible mechanisms for this transformation can be invoked to explain the experimental results. In the first mechanistic pathway keto-aldehyde **118** tautomerizes to the enolic form **119** and adds in a Michael fashion in to the ynone **104** forming an alleneol **120** which undergoes aldol addition in to the proximal aldehyde. Dehydration forms protected vinaxanthone **114**. In the second pathway, keto-aldehyde **118** tautomerizes to the dienol **121** which participates in a regioselective Diels-Alder cycloaddition with ynone **104**. Analogously, dehydration forms protected vinaxanthone **114** (Figure 48).

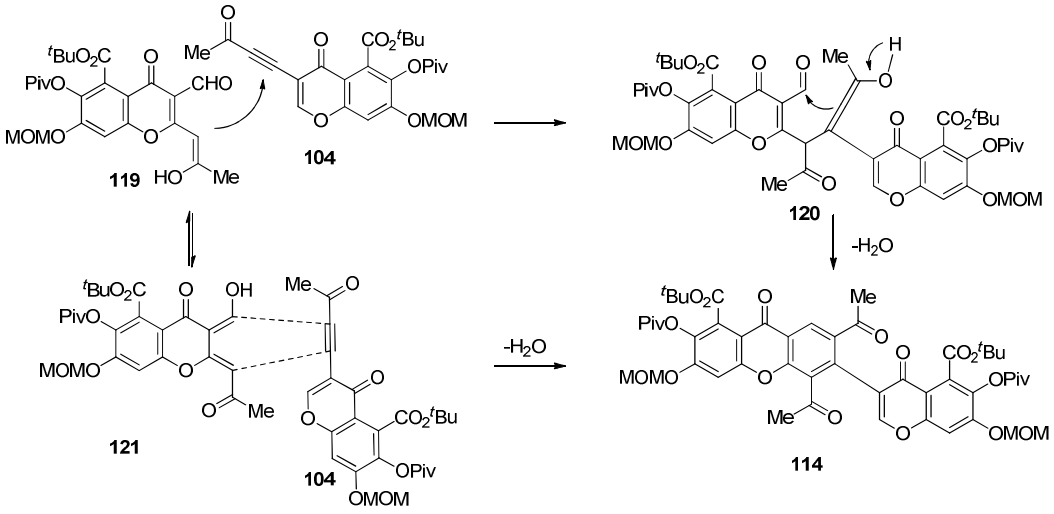


Figure 48. Mechanistic rationale in the dimerization reaction of ynone **108** to furnish protected vinaxanthone **116**.

It is speculated that the Diels-Alder pathway is operative. The low pKa of the ketonic protons should allow for facile dienol formation and the resultant enol should hydrogen bond to the ketone of the chromanone. This pathway has also been used to furnish a cycloadduct of keto-aldehyde and DMAD. This transformation only works with doubly-activated alkynes (Figure 49).

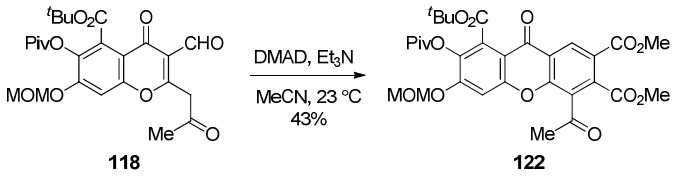
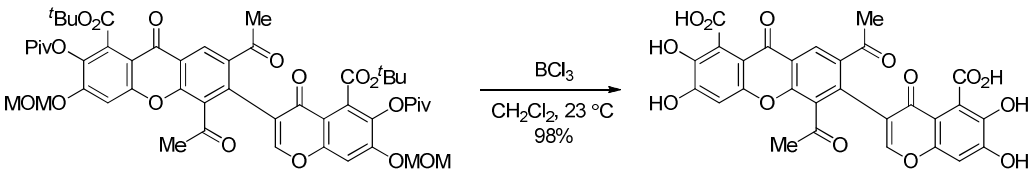


Figure 49. Adduct formation **122** with keto-aldehyde **118** and DMAD.

Mono-activated alkynes fail to react productively, giving low yields of recovered keto-aldehyde **118** with polymeric side products. This reactivity is being used to synthesize analogs to be used in biological testing.

With several methods for the synthesis of protected vinaxanthone **114**, the remaining goal was to simultaneously remove all phenolic and carboxylic acid protecting

groups. This was accomplished with BCl_3 in methylene chloride at room temperature, furnishing synthetic vinaxanthone (**1**) which matched all previously reported spectroscopic values (Figure 50).[42-44]



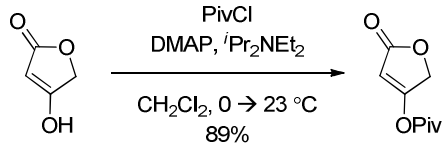
114 vinaxanthone (**1**)

Figure 50. Synthesis of vinaxanthone (**1**).

Experimental Section - General Information

All reactions were performed in flame dried round bottom or modified Schlenk (Kjedahl shape) flasks fitted with rubber septa under a positive pressure of argon, unless otherwise indicated. Air-and moisture-sensitive liquids and solutions were transferred by syringe or canula. Where necessary (so noted), solutions were deoxygenated by alternative freeze (liguid-N_2)/evacuation/thaw cycles (> three iterations). Organic solutions were concentrated by rotary evaporation at ~ 20 torr. Dichloromethane (CH_2Cl_2), tetrahydrofuran (THF) were purified using a Pure-Solv MD-5 Solvent Purification System (Innovative Technology). Acetonitrile (MeCN) was purified using a Vac 103991 Solvent Purification System (Vacuum Atmospheres). Dimethoxyethane (DME) was purchased from Acros (99+%, stabilized with BHT), N,N-dimethylformamide (DMF) was purchased from Acros (99.8%, anhydrous), methanol (MeOH) was purchased from Sigma-Aldrich (99.8%, anhydrous), ethanol (EtOH) was purchased from Pharmco-Aaper (200 proof, absolute). Chloromethyl methyl ether was prepared according to the method of Berliner.[1] The method of Corey was used to prepare *tert*-butyldimethylsilyl triflate.[2] All other reagents were used directly from the supplier without further purification unless noted. Analytical thin-layer chromatography (TLC) was carried out using 0.2 mm commercial silica gel plates (silica gel 60, F254, EMD chemical) and visualized using a UV lamp and or ceric ammonium molybdate (CAM) or aqueous potassium permanganate ($KMnO_4$) stain. Infrared spectra were recorded on a Nicolet 380 FTIR using neat thin film technique. High-resolution mass spectra (HRMS) were recorded on a Karatos MS9 and are reported as m/z (relative intensity). Accurate

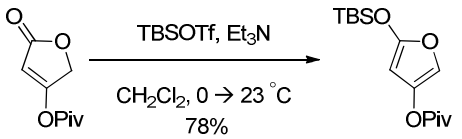
masses are reported for the molecular ion $[M+Na]^+$, [M+H], $[M^+]$, or [M-H]. Nuclear magnetic resonance spectra (^{1}H NMR and ^{13}C NMR) were recorded with a Varian Gemini [(400 MHz, ^{1}H at 400 MHz, ^{13}C at 100 MHz), (500 MHz, ^{13}C at 125 MHz), (600 MHz, ^{13}C at 150 MHz)]. For $CDCl_3$ and CD_3OD solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; $CHCl_3$ δ H (7.26 ppm) and $CDCl_3$ δ D (77.0 ppm) or CHD_2OD δ H (3.34 ppm) or CD_3OD δ C (49.0 ppm). For CD_2Cl_2 and $(CD_3)_2SO$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; CH_2Cl_2 δ H (5.32 ppm) and CD_2Cl_2 δ D (53.8 ppm) or $(CH_3)_2SO$ δ H (2.50 ppm) or $(CD_3)_2SO$ δ C (39.5 ppm). For C_6D_6 and $(CD_3)_2CO$ solutions the chemical shifts are reported as parts per million (ppm) referenced to residual protium or carbon of the solvents; C_6H_6 δ H (7.16 ppm) and C_6D_6 δ D (128.1 ppm) or $(CH_3)_2CO$ δ H (2.05 ppm) and $(CD_3)_2CO$ δ D (205.87 ppm for CO and 30.60 for CD_3). Coupling constants are reported in Hertz (Hz). Data for ^{1}H-NMR spectra are reported as follows: chemical shift (ppm, referenced to protium; s = singlet, d = doublet, t = triplet, q= quartet, dd = doublet of doublets, td = triplet of doublets, ddd = doublet of doublet of doublets, m = multiplet, coupling constant (Hz), and integration). Melting points were measured on a MEL-TEMP device without corrections.



73 **74**

To a stirred solution of tetronic acid **73** (25.0 g, 250 mmol, 1.0 equiv.), 4-dimethylaminopyridine, (1.53 g, 12.5 mmol, 0.05 equiv.) and N,N-diisopropylethylamine (45.8 mL, 262 mmol, 1.05 equiv.) in CH_2Cl_2 (500 mL) at 0 °C was added neat pivaloyl chloride (25.9 mL, 262 mmol, 1.05 equiv.) dropwise over 40 minutes. Upon complete addition the dark-brown solution was allowed to warm to 23 °C. After 16 hours the reaction mixture was concentrated *in vacuo* to give a dark-brown oil. The residue was suspended in Et_2O (500 mL) and washed with H_2O (500 mL). The aqueous layer was extracted with Et_2O (5 x 500 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to give **74** (41.0 g, 223 mmol, 89%) as clear-amber crystals (m.p. 46-47 °C).

R_f = 0.60 (silica gel, 1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.00 (t, *J* = 1.4 Hz, 1H), 4.91 (d, *J* = 1.4 Hz, 2H), 1.32 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 173.2, 172.2, 169.1, 100.2, 68.2, 38.3, 26.4; **IR** (film, υ cm^{-1}): 1779, 1746, 1072; **m.p.**: 46-47 °C.

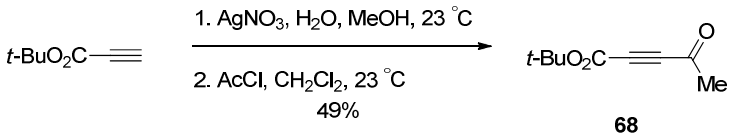


74 **72**

To a stirred solution of **74** (30.0 g, 163 mmol, 1.0 equiv.) in CH_2Cl_2 (226 mL) at 0 °C was added triethylamine (29.8 mL, 212 mmol, 1.3 equiv.) in one portion. Neat *tert*-butyldimethylsilyl triflate (37.8 mL, 165 mmol, 1.01 equiv.) was then added dropwise over 10 minutes. Upon complete addition the amber solution was allowed to warm to 23 °C. After 1 hour the reaction mixture was concentrated *in vacuo* to give an amber oil. The residue was suspended in pentane (200 mL) and stirred for 1 hour. The organic layer was washed with sat. aq. $NaHCO_3$ (100 mL), passed over solid $NaHCO_3$ (10 g), filtered and washed with brine (100 mL). The organic layer was dried over potassium caronate and concentrated *in vacuo* to give furan **72** (37.9 g, 127 mmol, 78%).

R_f = 0.55 (silica gel, 20:1 hexanes:EtOAc); **^{1}H NMR** (300 MHz, $CDCl_3$): δ 7.10 (d, *J* = 1.2 Hz, 1H), 5.15 (d, *J* = 1.2 Hz, 1H), 1.29 (s, 9H), 0.96 (s, 9H), 0.24 (s, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.3, 154.3, 139.4, 120.6, 80.1, 39.0, 27.1, 25.4, 18.0, -4.85; **IR** (film, υ cm $^{-1}$): 3202, 3141, 1753, 1627; **HRMS** (ESI) calc. for $C_{15}H_{27}O_4Si$ $[M+H]^+$: 299.20000. Found: 299.20000.

Preparation #1[18,19]

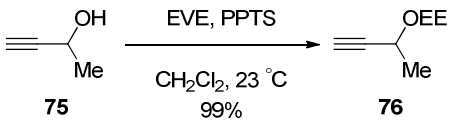


68

To a base-washed flask was added silver nitrate (5.39 g, 31.7 mmol, 2.0 equiv.) water (60 mL) and MeOH (30 mL). Ammonium hydroxide was added dropwise (initially turning the solution into a dark brown heterogeneous solution) until the precipitate dissolved and the color dissipated. The flask was protected from light and purged with argon. To this vigorously stirred solution was added *tert*-butyl propiolate (2.18 mL, 15.85 mmol, 1.0 eq.) as a solution in MeOH (10 mL) over 2 hours. The milky solution stirred for an additional 2 hours at 23 °C. The solution was poured into a separatory funnel, and extracted with CCl_4 once and chloroform three times. The combined organics were then washed with water three times, dried over $CaCl_2$ and concentrated to reveal a brown/white solid. The solid was then diluted in CH_2Cl_2 (21 mL) and protected from light. Acetyl chloride (1.13mL, 15.85 mmol, 1 eq.) was added as a solution in CH_2Cl_2 (10 mL). The solution stirred at 23 °C for 20 hours. The heterogeneous solution was diluted with diethyl ether, and the solids were filtered off. The ethereal layer was washed twice with pH 7 buffer (0.2M phosphate), brine and then dried over $MgSO_4$. The solvent was removed yielding **27** as a brown, volatile liquid (1.25 g, 7.76 mmol, 49%).

R_f = 0.40 (silica gel, 10:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 1.52 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.8, 151.0, 85.4, 79.2, 79.0, 32.3, 27.9; **IR** (film, υ cm $^{-1}$) 1716, 1689; **HRMS** (EC-CI) calc. for $C_9H_{13}O_3$ $[M+H]^+$: 169.0865. Found 169.0866.

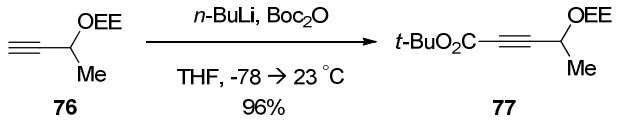
Preparation #2[20]



75 **76**

To a stirred solution of 3-butyn-2-ol **75** (100 g, 1.43 mmol, 1.0 equiv.) and ethyl vinyl ether (151 mL, 1.57 mol, 1.1 equiv.) in CH_2Cl_2 (3 L) at 23 °C was added pyridinium p-toluenesulfonate (35.9 g, 143 mmol, 0.1 equiv.) in one portion. After 1 hour the clear solution was diluted with Et_2O (1 L) and washed with brine (2 L). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give **76** as a mixture of diastereomers (201 g, 1.41 mol, 99%) as a clear oil.

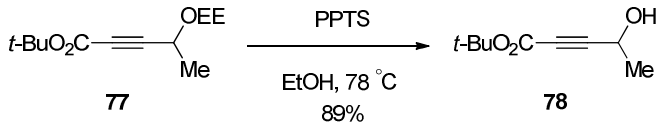
$\mathbf{R_f}$ = 0.40 (silica gel, 1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.96 (q, *J* = 5.5 Hz, 1H), 4.85 (q, *J* = 5.5 Hz, 1H), 4.50 (q, *J* = 6.7 Hz, 1H), 4.35 (q, *J* = 6.7 Hz, 1H), 3.75 (m, 1H), 3.62 (m, 1H), 3.53 (m, 2H), 2.40 (s, 1H), 2.39 (s, 1H), 1.46 (d, *J* = 3.1 Hz, 3H), 1.44 (d, *J* = 3.1 Hz, 3H), 1.35 (d, *J* = 2.7 Hz, 3H), 1.34 (d, *J* = 2.7 Hz, 3H), 1.21 (t, *J* = 7.0 Hz, 6H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 98.5, 97.5, 84.5, 83.6, 72.4, 72.0, 61.1, 60.5, 60.0, 59.9, 22.3, 21.9, 20.0, 19.9, 15.2, 14.9; **HRMS** (EC-CI) calc. for $C_8H_{13}O_2$ $[M+H]^+$: 141.0916. Found: 141.0918.



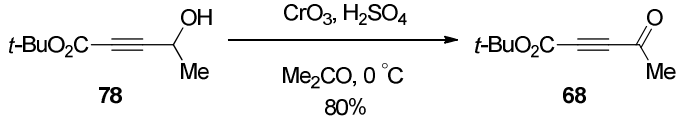
76 **77**

To a stirred solution of **76** (110 g, 774 mmol, 1.0 equiv.) in THF (4.5 L) at −78 °C was added a solution of *n*-butyllithium in hexanes (2.0 M, 404 mL, 808 mmol, 1.05 equiv.). After 15 minutes neat liquid di-*tert*-butyl dicarbonate (186 mL, 808 mmol, 1.05 equiv.) was added over 10 minutes. Upon complete addition the amber solution was allowed to warm to 23 °C. The reaction mixture was diluted with Et_2O (1.5 L) and washed with H_2O (3 L) and brine (3 L). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give **77** as a mixture of diasteromers as an amber oil (180 g, 743 mmol, 96%).

R_f = 0.21 (silica gel, 20:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.91 (q, *J* = 5.1 Hz, 1H), 4.82 (q, *J* = 5.1 Hz, 1H), 4.56 (q, *J* = 6.8 Hz, 1H), 4.40 (q, *J* = 6.8 Hz, 1H), 3.73 (m, 1H), 3.62 (m, 1H), 3.56 (m, 1H), 3.50 (m, 1H), 1.49 (s, 18 H), 1.46 (d, *J* = 1.7 Hz, 6H), 1.34 (d, *J* = 1.4 Hz, 6H) 1.12 (t, *J* = 8.5 Hz, 6H); **^{13}C NMR** (100 MHz, C_6D_6): δ 152.6, 152.5, 99.3, 98.3, 86.1, 85.2, 82.9, 82.7, 78.3, 77.9, 61.0, 60.4, 60.3, 60.2, 27.8 (2 signals), 21.8, 21.5, 20.1, 20.0, 15.5, 15.3; **IR** (film, υ cm $^{-1}$): 1710, 1274, 1160; **HRMS** (ESI) calc. for $C_{13}H_{22}NaO_4$ $[M+Na]^+$: 265.14103. Found: 265.14100.

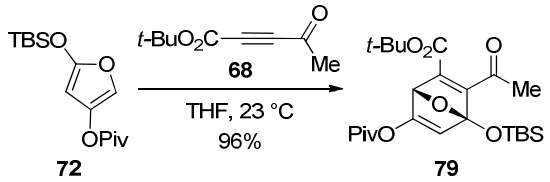


To a stirred solution of **77** (117g, 483 mmol, 1.0 equiv.) in EtOH (4.8 L) at 78 °C was added pyridinium p-toluenesulfonate (12.1g, 48.3 mmol, 0.1 equiv.) in one portion. After 2 hours the amber solution was allowed to cool to 23 °C. The reaction mixture was diluted with Et_2O (2.4 L) and washed with brine (4 L). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to give **78** (73.1 g, 429 mmol, 89%) as an amber oil. **R_f** = 0.30 (silica gel, 3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 4.62 (m, 1H), 2.13 (s, 1H), 1.51 (m, 12H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 152.8, 86.8, 82.9, 77.5, 57.8, 27.8, 23.1; **IR** (film, υ cm $^{-1}$): 3400, 1709; **HRMS** (EC-CI) calc. for $C_9H_{15}O_3$ $[M+H]^+$: 171.1021. Found: 171.1019.



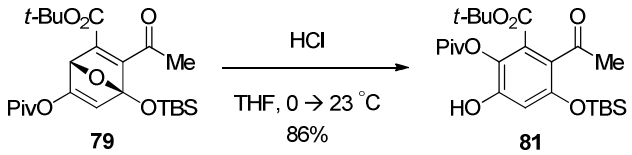
To a stirred solution of **78** (73.0 g, 429 mmol, 1.0 equiv.) in Me_2CO (1.2 L) at 0 °C was added ice-cold Jones reagent (1.53 M (67.0 g CrO_3, 58.0 mL conc. H_2SO_4 and 160 mL H_2O), 280 mL, 429 mmol, 1.0 equiv.) slowly over 15 mintues. After 30 minutes the ^{i}PrOH (40 mL) was added to neutralize any excess Jones reagent. The reaction mixture was diluted with CH_2Cl_2 (1 L) and filtered through silica gel (100 g) with 1:1 pentane:Et_2O (2 L). The filtrate was washed with H_2O (1 L), sat. aq. $NaHCO_3$ (1 L) and brine (1 L). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give keto-ester **68** (57.5 g, 342 mmol, 80%) as a clear-amber oil.

R_f = 0.40 (silica gel, 10:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 2.41 (s, 3H), 1.52 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 182.8, 151.0, 85.4, 79.2, 79.0, 32.3, 27.9; **IR** (film, υ cm $^{-1}$): 1716, 1689; **HRMS** (EC-CI) calc. for $C_9H_{13}O_3$ $[M+H]^+$: 169.0865. Found: 169.0866.



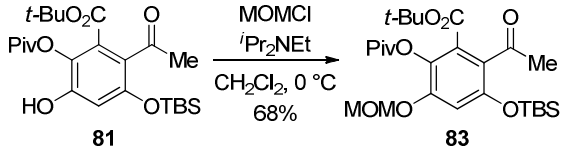
To a stirred solution of furan **72** (70.4 g 236 mmol, 1.0 equiv.) in THF (212 mL) at 0 °C was added keto ester **68** (39.7 g, 236 mmol, 1.0 equiv.) in one portion. Upon complete addition the amber solution was allowed to warm to 23 °C. After 1 hour the reaction mixture was concentrated *in vacuo* to give **79** as a clear yellow oil.

R_f = 0.35 (silica gel, 10:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.38 (s, 1H), 5.24 (s, 1H), 2.43 (s, 3H), 1.47 (s, 9H), 1.25 (s, 9H), 0.90 (s, 9H), 0.20 (s, 3H), 0.18 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 199.3, 174.3, 167.7, 163.7, 161.2, 146.3, 118.5, 113.9, 82.3, 78.2, 39.2, 30.7, 27.9, 26.8, 25.4, 17.7, -3.5, -3.7; **IR** (film, υ cm $^{-1}$): 1769, 1712; **HRMS** (EC-CI) calc. for $C_{24}H_{38}O_7Si$ $[M+Na]^+$: 489.22790. Found: 489.22801.



To a stirred solution of bicycle **79** (110 g, 236 mmol, 1.0 equiv.) in THF (471 mL) at 0 °C was added a solution of dry hydrochloric acid in dioxane (4.0 M, 47.1 mL, 47.1 mmol, 0.2 equiv.) slowly over 5 minutes. Upon complete addition the amber solution was allowed to warm to 23 °C. After 2 hours the reaction mixture was concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography (20:1 hexanes:EtOAc) to give phenol **81** (82.9 g, 178 mmol) as a clear, slightly yellow oil.

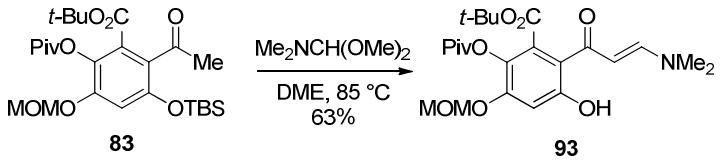
R_f = 0.38 (silica gel, 10:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 10.91 (s, 1H), 6.71 (s, 1H), 2.48 (s, 3H), 1.54 (s, 9H), 1.38 (s, 9H), 0.94 (s, 9H), 0.18 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 202.3, 176.3, 168.4, 148.7, 142.5, 139.7, 131.9, 119.9, 111.0, 85.7, 39.2, 32.5, 27.8, 27.2, 25.5, 18.0, -4.4; **IR** (film, υ cm^{-1}): 1763, 1716, 1673; **HRMS** (EC-CI) calc. for $C_{24}H_{38}O_7Si$ $[M+Na]^+$: 489.22790. Found: 489.22813.



81 **83**

To a stirred solution of phenol **81** (82.9 g, 178 mmol, 1.0 equiv.) in CH_2Cl_2 (1.7 L) at 0 °C was added N,N-diisopropylamine (63.4 mL, 355 mmol, 2.0 equiv.). A solution of methoxymethyl chloride in PhMe/MeOAc (2.1 M, 127 mL, 267 mmol, 1.5 equiv.) was then added slowly over 20 minutes. Upon complete addition the amber solution was allowed to warm to 23 °C. After 1 hour the reaction mixture was diluted with 0.1 M HCl (500 mL) and extracted with CH_2Cl_2 (500 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography (10:1 hexanes:EtOAc) to give acetophenone **83** (61.4 g, 120 mmol, 68%) as a white solid (m.p. 60-62 °C).

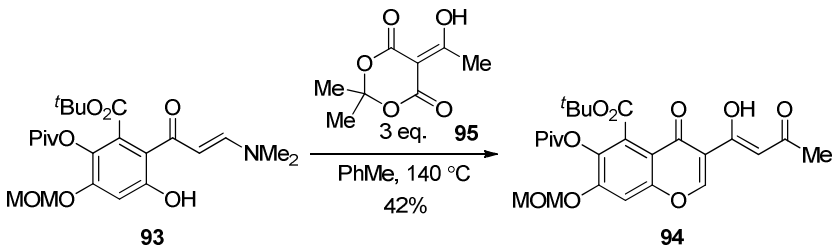
R_f = 0.61 (silica gel, 3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 6.76 (s, 1H), 5.10 (s, 2H), 3.42 (s, 3H), 2.54 (s, 3H), 1.49 (s, 9H), 1.34 (s, 9H), 0.97 (s, 9H), 0.21 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 200.9, 175.7, 163.5, 150.9, 150.4, 132.8, 128.1, 125.7, 108.6, 94.6, 82.5, 55.9, 38.9, 31.7, 27.7, 27.1, 25.6, 18.1, -4.4; **IR** (film, υ cm $^{-1}$): 1761, 1733, 1703; **HRMS** (ESI) calc. for $C_{26}H_{42}NaO_8Si$ $[M+Na]^+$: 533.25412. Found 533.25387; **m.p.**: 60-62 °C.



83 **93**

To a stirred solution of acetophenone **83** (15.4 g, 30.2 mmol, 1.0 equiv.) in DME at 85 °C was added N,N-dimethylformamide dimethyl acetal (16.1 mL, 121 mmol, 4.0 equiv.) in one portion. After 3 hours the amber solution was cooled to 23 °C and then concentrated *in vacuo* to give enaminone **93** as a dark amber oil of sufficient purity for subsequent steps. However, when the crude material was purified via silica gel column chromatography (1:1 hexanes:EtOAc) enaminone **93** (8.59 g, 19.0 mmol, 63%) was obtained as an orange solid (m.p. 118-119 °C).

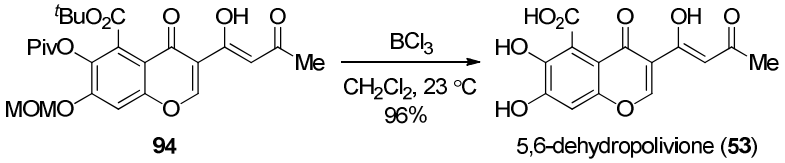
R_f = 0.26 (silica gel, 1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 12.43 (bs, 1H), 7.77 (d, *J* = 12.2 Hz, 1H), 6.70 (s, 1H), 5.49 (d, *J* = 12.2 Hz, 1H), 5.13 (s, 2H), 3.41 (s, 3H), 3.15 (s, 3H), 2.84 (s, 3H), 1.47 (s, 9H), 1.34 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 189.4, 175.8, 165.6, 159.3, 154.4, 151.6, 130.1, 128.5, 113.7, 104.0, 95.2, 94.0, 82.4, 56.0, 45.1, 38.7, 37.1, 27.6, 27.0; **IR** (film, υ cm $^{-1}$): 1751, 1716, 1632, 1111; **HRMS** (ESI) calc. for $C_{23}H_{33}NNaO_8$ $[M+Na]^+$: 474.20984. Found: 474.21058; **m.p.**: 118-119 °C.



To a solution of **93** (1.44 g, 3.19 mmol, 1.0 eq.) in toluene (32 mL) was added freshly ground acyl Meldrum's acid **95** (1.78 g, 9.57 mmol, 3.0 eq.). The amber solution was heated to 110 °C for 45 minutes then cooled to 23 °C and concentrated *in vacuo* to give a brown solid. The crude material was purified via acidified silica gel* column chromatography (7:1 hexanes: EtOAc), yielding **94** (650 mg, 1.33 mmol, 42%) as a yellow solid (m.p. = 181-182 °C).

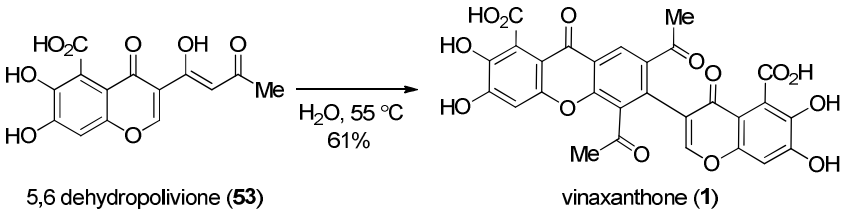
R_f = 0.24 (silica gel, 3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 15.87 (s, 1H), 8.66 (s, 1H), 7.23 (s, 1H), 7.05 (s, 1H), 5.24 (s, 2H), 3.45 (s, 3H), 2.22 (s, 3H), 1.65 (s, 9H), 1.38 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$, The highly concentrated ^{13}C sample produced a mixture of keto and enol tautomers) δ 202.5, 197.6, 192.1, 174.3, 172.6, 163.6, 161.7, 159.4, 154.5, 154.2, 153.4, 136.7, 128.6, 120.9, 118.0, 116.3, 115.8, 103.9, 103.8, 101.7, 94.7, 83.1, 57.7, 56.7, 56.6, 39.2, 30.7, 28.2, 27.2, 26.9; **IR** (film, cm $^{-1}$) 1762, 1734, 1663, 1621; **HRMS** (ESI) calcd. for $C_{25}H_{30}NaO_{10}$ $[M+Na]^+$ 513.17312 found 513.17341.

*To a 4 L Erlenmeyer flask was added 400 g of silica gel. Added was 2.50 L of deionized water and the slurry stirred vigorously. The solution was acidified to a pH of 2 with 6.50 mL of 85% phosphoric acid. The slurry stirred for 20 minutes. The silica gel was filtered and washed with ethyl acetate, then dried in a 120 °C oven overnight.



94 5,6-dehydropolivione (**53**)

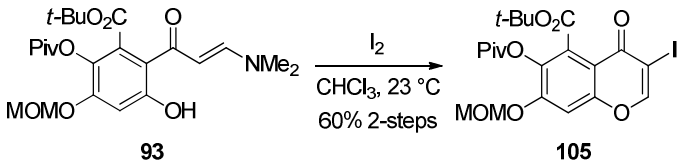
To a solution of **94** (50.0 mg, 0.102 mmol, 1.0 equiv.) in CH_2Cl_2 (10 mL) 0 °C was added boron trichloride solution (1.0 M in CH_2Cl_2, 1.22 mmol, 1.22 mL, 12.0 equiv.). The red heterogeneous solution was warmed to 23 °C and stirred for 1 hour. The reaction was then cooled to 0 °C and quenched with 2 mL of 2N HCl, and stirred at 0 °C for 5 minutes. The solution was diluted with ethyl acetate (30 mL) and the pH of the aqueous layer was adjusted to a pH of 7 using a pH 10 buffer (40 mL of 0.2 M phosphate buffer). The layers were separated and the organic layer was extracted three times with additional pH 7 buffer (30 mL of 0.2 M phosphate buffer). The combined aqueous washes were re-acidified to a pH of 2 using 2N HCl and extracted with ethyl acetate (3 x 30 mL). The organic layers were washed with brine (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to yield 5,6-dehydropolivione (**53**) (20.1 mg, 0.098 mmol, 96% yield) as a yellow solid (m.p. = 231-232 °C). $\mathbf{R_f}$**=** 0.54 (silica gel, 90:10 EtOAc:AcOH); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ [enol] 16.10 (bs, 1H), 12.71 (bs, 1H), 11.55 (bs, 1H), 9.50 (bs, 1H), 8.84 (s, 1H), 6.98 (s, 1H), 6.96 (s, 1H), 2.19 (s, 3H), [keto] 12.71 (bs, 1H), 11.55 (bs, 1H), 9.50 (bs, 1H), 8.73 (s, 1H), 6.96 (s, 1H), 4.09 (s, 2H), 2.20 (s, 3H); **^{13}C NMR** (100 MHz, $(CD_3)_2SO$) δ [enol] 196.7, 176.0, 172.3, 167.4, 160.2, 152.6, 149.8, 142.0, 120.2, 116.2, 113.2, 102.4, 100.8, 26.3, [keto] 203.0, 192.7, 173.0, 161.7, 152.6, 150.1, 120.4, 120.2, 113.6, 102.5, 57.4, 30.6; **IR** (film, cm $^{-1}$) 3280, 1617, 1473; **HRMS** (ESI) calcd. for $C_{14}H_9O_8$ $[M-H]^-$ 305.03029 found 305.03013.



5,6 dehydropolivione (**53**) vinaxanthone (**1**)

5,6-dehydropolivione (**53**) (10.0 mg, 0.033 mmol, 1.00 eq) in water (0.327 mL) stirred at 55 °C for 4 days. The reaction was quenched with 2 mL of conc. ammonium hydroxide. The solution was washed with ethyl acetate (2 x 20 mL), and then re-acidified to a pH of 1 using conc. HCl at 0 °C. The crude material was extracted with ethyl acetate (3 x 20 mL), washed with pH 2 buffer (20 mL), then brine (30 mL) before drying over magnesium sulfate, yielding vinaxanthone (**1**), (5.7 mg, 0.0099 mmol, 61%) as a yellow solid after trituration with methanol (3 x 1mL portions).

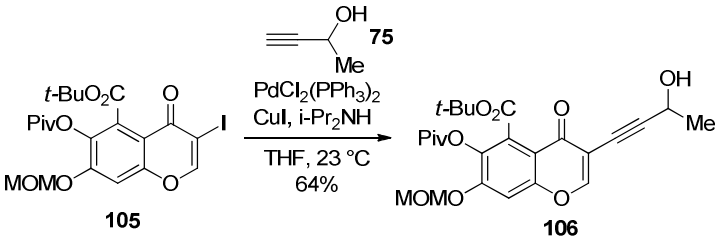
R_f= 0.05 (sílica gel, 95:5 EtOAc:AcOH); **^{1}H NMR** (400 MHz, $(CD_3)_2SO$) δ 12.89 (bs, 1H), 12.72 (bs, 1H), 11.69 (bs, 1H), 11.44 (bs, 1H), 9.42 (bs 2H), 9.42 (bs, 2H), 8.53 (s, 1H), 8.18 (s, 1H), 6.96 (s, 1H), 6.94 (s, 1H), 2.55 (s, 3H), 2.53 (s, 3H); **^{13}C NMR** (125 MHz, $(CD_3)_2SO$) δ 201.1, 199.1, 172.9, 172.6, 167.4, 167.4, 154.1, 152.7, 152.5, 152.1, 150.7, 150.3, 141.7, 141.0, 136.2, 133.4, 132.6, 126.3, 120.8, 120.5, 119.8, 119.6, 112.4, 110.0, 102.4, 102.3, 32.1, 29.1; **IR** (KBr, cm $^{-1}$) 3236, 1683, 1653, 1472, 1288; **HRMS** (ESI) calc. For $C_{28}H_{15}O_{14}$ $[M-H]^-$: 575.04673, obs. 575.04679; **m.p.** >280 °C.



93 **105**

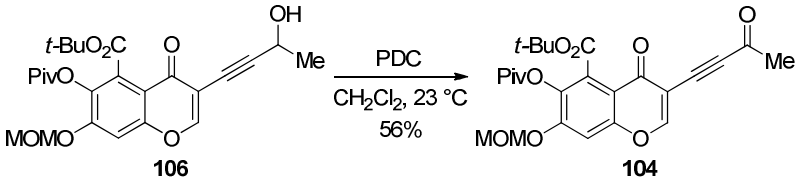
To a stirred solution of enaminone **93** (13.6 g, 30.2 mmol, 1.0 equiv.) in $CHCl_3$ (302 mL) at 23 °C was added solid iodine (15.3 g, 60.4 mmol, 2.0 equiv.) in one portion. After 3 hours the black solution was diluted with aq. sat. $Na_2S_2O_3$ (300 mL) and extracted with CH_2Cl_2 (300 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give a tan solid. The crude material was purified via silica gel column chromatography (1:1 hexanes:EtOAc) to give iodochromone **105** (9.97 g, 18.7 mmol, 62%; 9.65 g, 18.1 mmol, 60% over 2 steps) as a white solid (m.p. 189-190 °C).

R_f = 0.32 (silica gel, 3:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.17 (s, 1H), 5.23, (s, 2H), 3.25 (s, 3H), 1.64 (s, 9H), 1.37 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.4, 170.9, 163.2, 156.8, 154.9, 153.3, 136.5, 128.3, 112.8, 103.5, 94.7, 86.7, 83.3, 56.6, 39.2, 28.2, 27.2; **IR** (film, υ cm^{-1}): 1764, 1731, 1650; **HRMS** (ESI) calc. for $C_{21}H_{25}INaO_8$ $[M+Na]^+$: 555.04863. Found: 555.04881; **m.p.**: 189-190 °C.



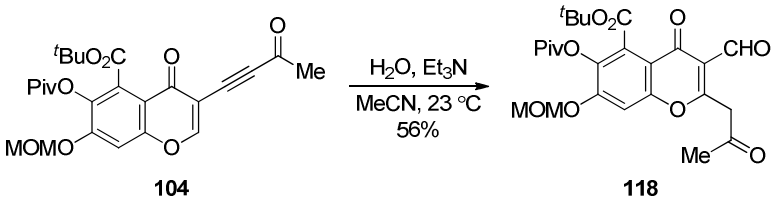
To a stirred solution of iodochromone **105** (3.0 g, 5.64 mmol, 1.0 equiv.), bis(triphenylphosphine) palladium (II) dichloride (396 mg, 0.56 mmol, 0.1 equiv.) and copper iodide (107 mg, 0.56 mmol, 0.1 equiv.) in degassed THF (56 mL) at 23 °C was added 3-butyn-2-ol **75** (1.8 mL, 22.5 mmol, 4.0 equiv.). Neat diisopropylamine (2.4 mL, 16.9 mmol, 3.0 equiv.) was then added. After 1 hour the reaction mixture was diluted with pH = 7.0 phosphate buffer (50 mL) and extracted with CH_2Cl_2 (50 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography (1:1 hexanes:EtOAc) to give propargyl alcohol **106** (1.71 g, 3.60 mmol, 64%) as a tan solid (m.p. 132-134 °C).

R_f = 0.21 (silica gel, 1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.03 (s, 1H), 7.14 (s, 1H), 5.21 (s, 2H), 4.75 (m, 1H), 3.43 (s, 3H), 3.20 (bs, 1H), 1.63 (s, 9H), 1.51 (d, *J* = 6.7 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 175.5, 173.3, 163.3, 157.5, 154.6, 153.2, 136.3, 128.1, 114.5, 110.5, 103.8, 97.5, 94.6, 83.2, 73.8, 58.6, 56.6, 39.2, 28.2, 27.2, 23.8; **IR** (film, υ cm^{-1}): 3435, 1763, 1735, 1731, 1461; **HRMS** (ESI) calc. for $C_{25}H_{30}NaO_9$ $[M+Na]^+$: 497.1782. Found: 497.1785; **m.p.**: 132-134 °C.



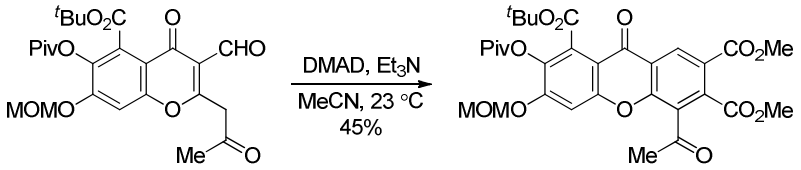
To a stirred solution of propargyl alcohol **106** (5.0 g, 10.5 mmol, 1.0 equiv.) and activated 4.0 Å molecular sieves (2 g) in CH_2Cl_2 (105 mL) at 23 °C was added solid pyridinium dichromate (19.0 g, 52.7 mmol, 5.0 equiv.) in one portion. After 2 hours the black solution was filtered through a pad of Celite™ and concentrated *in vacuo* to give an amber oil. The crude material was purified via silica gel column chromatography (1:1 hexanes:EtOAc) to give ynone **104** (2.79 g, 5.90 mmol, 56%) as a white solid (m.p. 178-179 °C).

R_f = 0.41 (silica gel, 1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.20 (s, 1H), 7.21 (s, 1H), 5.24 (s, 2H), 3.44 (s, 3H), 2.46 (s, 3H), 1.64 (s, 9H), 1.37 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$): δ 184.2, 175.4, 172.1, 163.1, 160.4, 154.6, 153.7, 136.8, 128.3, 114.6, 108.7, 104.0, 94.7, 93.5, 83.5, 81.0, 56.7, 39.2, 32.7, 28.2, 27.2; **IR** (film, υ cm^{-1}): 1762, 1734, 1672, 1620, 1459, 1264, 1246, 1155, 1091; **HRMS** (ESI) calc. for $C_{25}H_{28}NaO_9$ $[M+Na]^+$: 495.1626. Found: 495.1632; **m.p.:** 182-183 °C.



104 **118**

To a stirred solution of **104** (50 mg, 0.106 mmol, 1.0 equiv.) in MeCN (10.6 mL) at 23 °C was added H_2O (1.91 mL, 106 mmol, 1000 equiv.). Neat triethylamine (150 *u*L, 1.51 mmol, 10 equiv.) was then added. After 1 hour the amber solution was dried over $MgSO_4$ and concentrated *in vacuo* to give keto-aldehyde **118** (29 mg, 0.059 mmol, 56%) as an amber solid (m.p. 178-179 °C (decomp)) of sufficient purity for subsequent steps. **R_f** = 0.23 (silica gel, 1:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 7.20 (s, 1H), 5.23 (s, 2H), 4.26 (bs, 2H), 3.45 (s, 3H), 2.38 (s, 3H), 1.64 (s, 9H), 1.39 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 200.0, 190.7, 175.4, 175.0, 168.5, 163.3, 154.5, 153.9, 136.7, 128.2, 117.4, 115.5, 104.1, 94.8, 83.4, 56.6, 47.5, 39.2, 30.7, 28.2, 27.2; **IR** (film, υ cm^{-1}) 3420, 1762, 1730, 1653, 1595, 1458, 1265, 1157, 1029; **HRMS** (ESI) calc. for $C_{25}H_{30}NaO_{10}$ $[M+Na]^+$: 513.17312, obs. 513.17312.



118 **122**

To a stirred solution of **118** (25 mg, 0.051 mmol, 1.0 equiv.) and dimethyl acetylenedicarboxylate (**15**) (31 *u*L, 0.255 mmol, 5.0 equiv.) in MeCN (0.5 mL) at 23 °C was added triethylamine (36 *u*L, 0.205 mmol, 5.0 equiv.). After 1 hour the black solution was concentrated *in vacuo* to give a black oil. The crude material was purified via silica gel column chromatography (2:1 hexanes:EtOAc) to give xanthone **122** (14 mg, 0.022 mmol, 45%) as a white solid (m.p. 194-195 °C).

R_f = 0.22 (silica gel, 2:1 hexanes:EtOAc); **^{1}H NMR** (400 MHz, C_6D_6) δ 8.91 (s, 1H), 6.75 (s, 1H), 4.67 (s, 2H), 3.69 (s, 3H), 3.39 (s, 3H), 3.09 (s, 3H), 2.45 (s, 3H), 1.78 (s, 9H), 1.40 (s, 9H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 199.1, 175.5, 172.8, 166.8, 164.7, 163.2, 154.9, 154.4, 153.8, 137.9, 136.1, 131.0, 130.9, 129.0, 125.1, 121.8, 112.6, 103.5, 94.8, 83.5, 56.8, 53.3, 52.9, 39.2, 32.2, 28.1, 27.2; **IR** (film, υ cm^{-1}) 1733, 1463, 1271, 1243, 1157, 1093; **HRMS** (ESI) calc. for $C_{31}H_{34}NaO_{13}$ $[M+Na]^+$: 637.18916, obs. 637.18894.

pivtetronate

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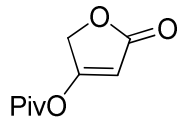
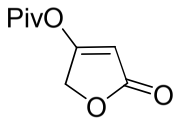


74

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pivtetronate

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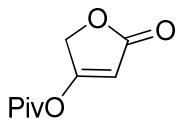

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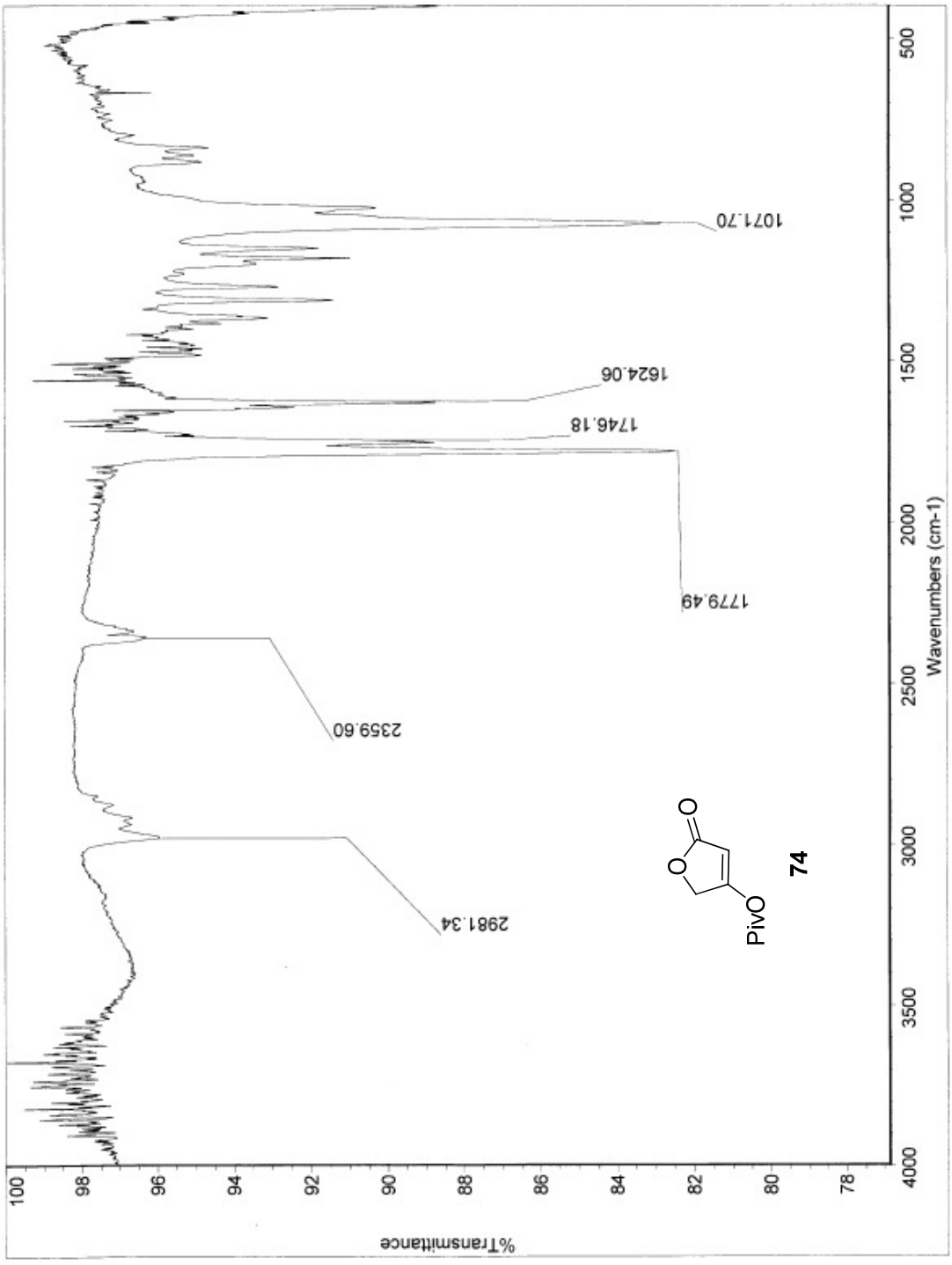
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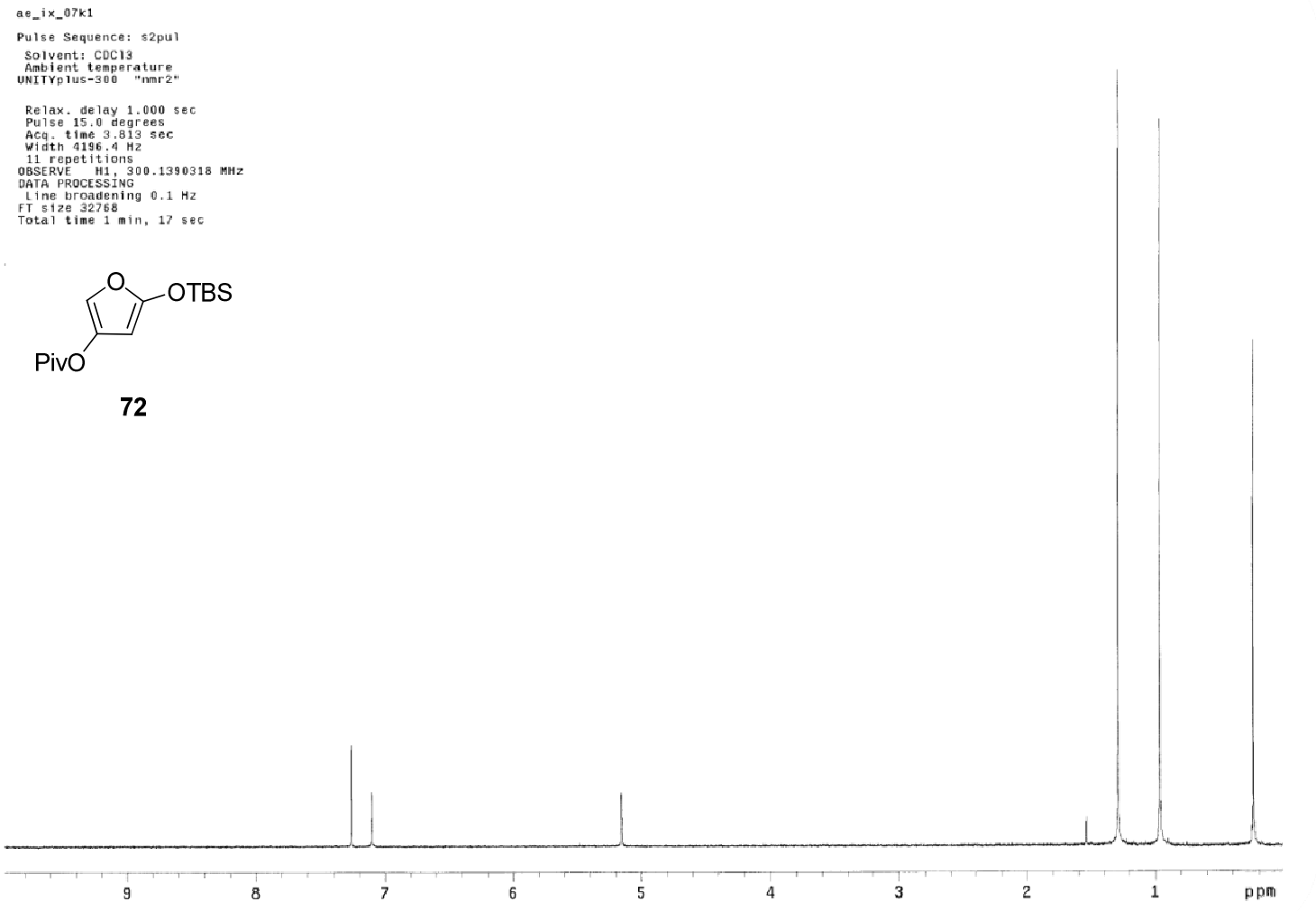
PivO
74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72

ae_ix_07

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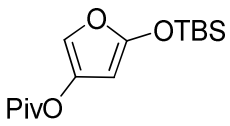
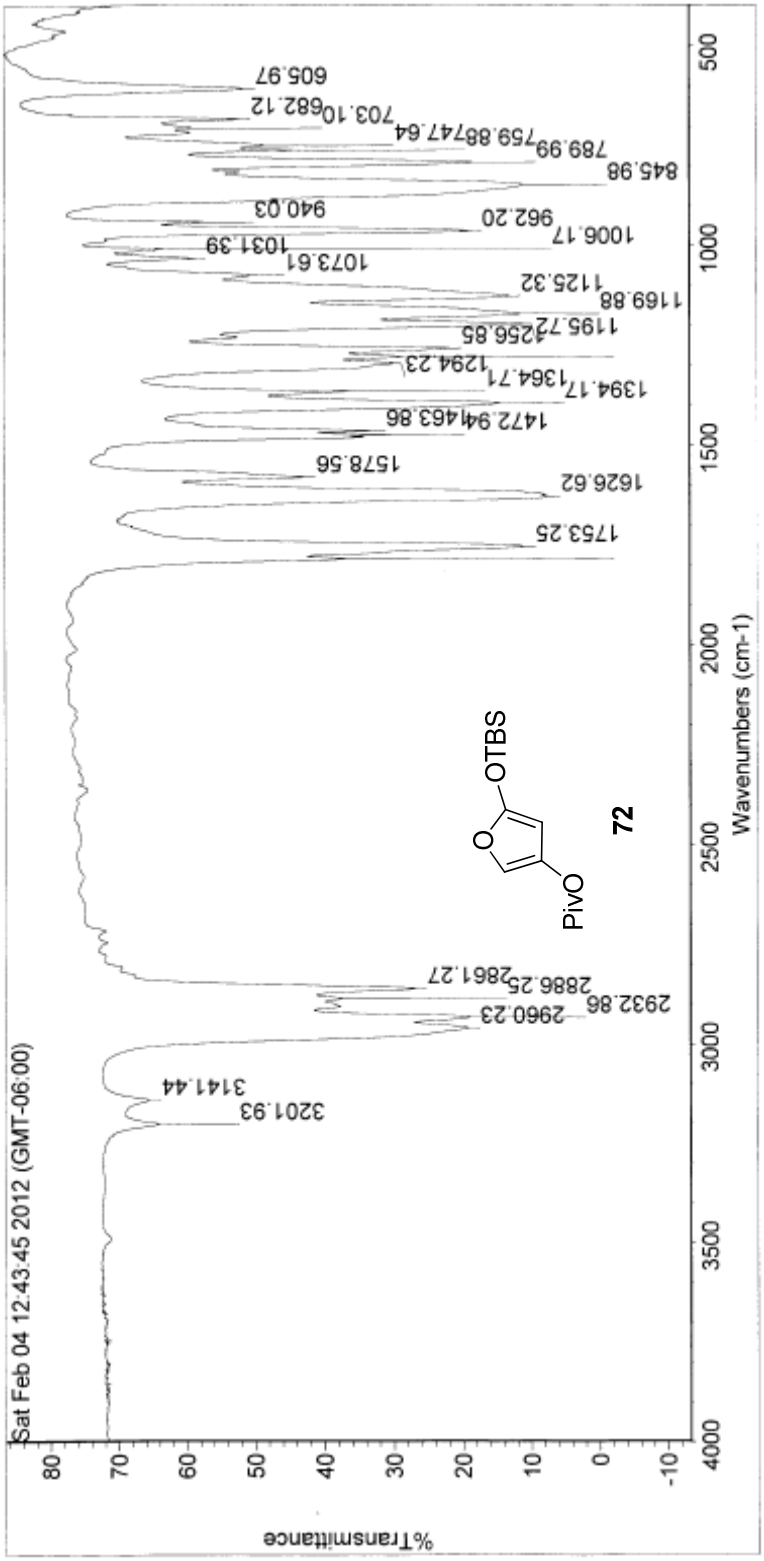
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
512 repetitions
OBSERVE C13, 100.5309749 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 42 sec



72


Sat Feb 04 12:43:45 2012 (GMT-06:00)
%Transmittance
Wavenumbers (cm-1)
OTBS
PivO
72
3201.93
3141.44
2960.23
2932.86
2886.25
2861.27
1753.25
1626.62
1578.56
1472.94
1463.86
1394.17
1364.71
1294.23
1256.85
1195.72
1169.88
1125.32
1073.61
1031.39
1006.17
962.20
940.03
845.98
789.99
759.88
747.64
703.10
682.12
605.97

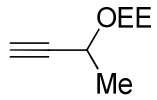
```
ae_viii_ee

 Archive directory: /home/staff31/vnmrsys/data
 Sample directory: ae_viii_ee_20120125_01

Pulse Sequence: s2pul

 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
File: PROTON_01
INOVA-500  "nmrfred"

 Relax. delay 2.000 sec
 Pulse 30.0 degrees
 Acq. time 2.556 sec
 Width 6410.3 Hz
 32 repetitions
OBSERVE   H1, 399.6763783 MHz
DATA PROCESSING
FT size 32768
Total time 2 min, 26 sec
```

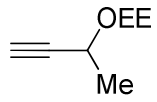


76

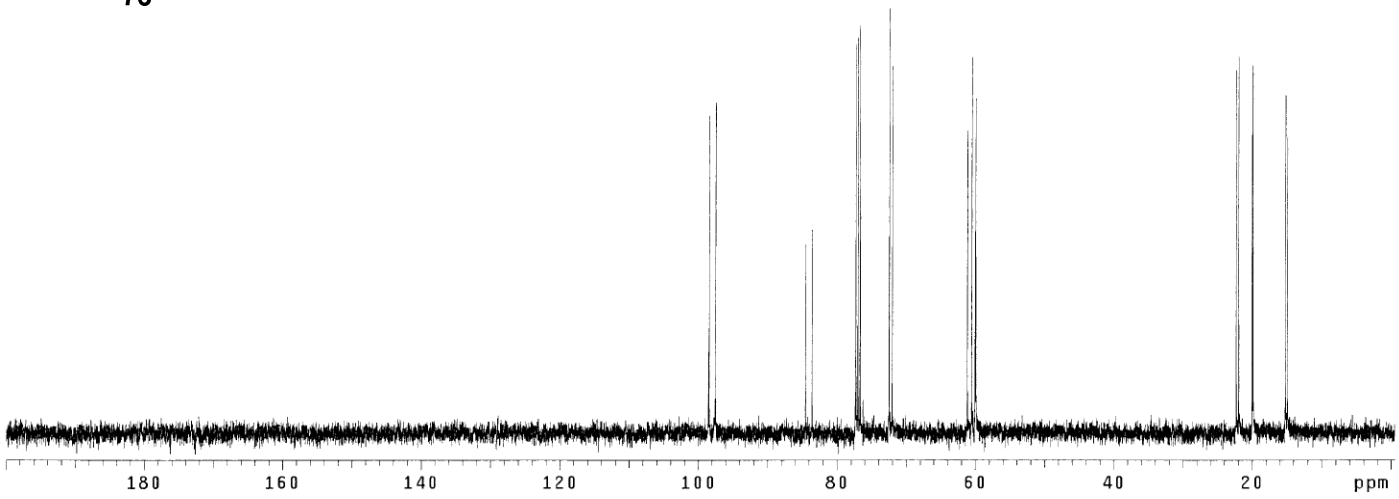
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

Relax. delay 2.000 sec
Pulse 22.5 degrees
Acq. time 1.280 sec
Width 25188.9 Hz
67 repetitions
OBSERVE C13, 100.6472207 MHz
DECOUPLE H1, 400.2689955 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 15 min, 38 sec



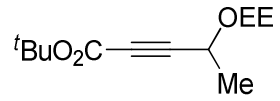
76



ae_viii_97p

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
16 repetitions
OBSERVE H1, 400.2669779 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 52 sec



77

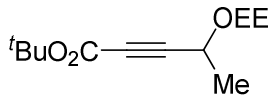
```
ae_viii_97

 Archive directory:
 Sample directory:

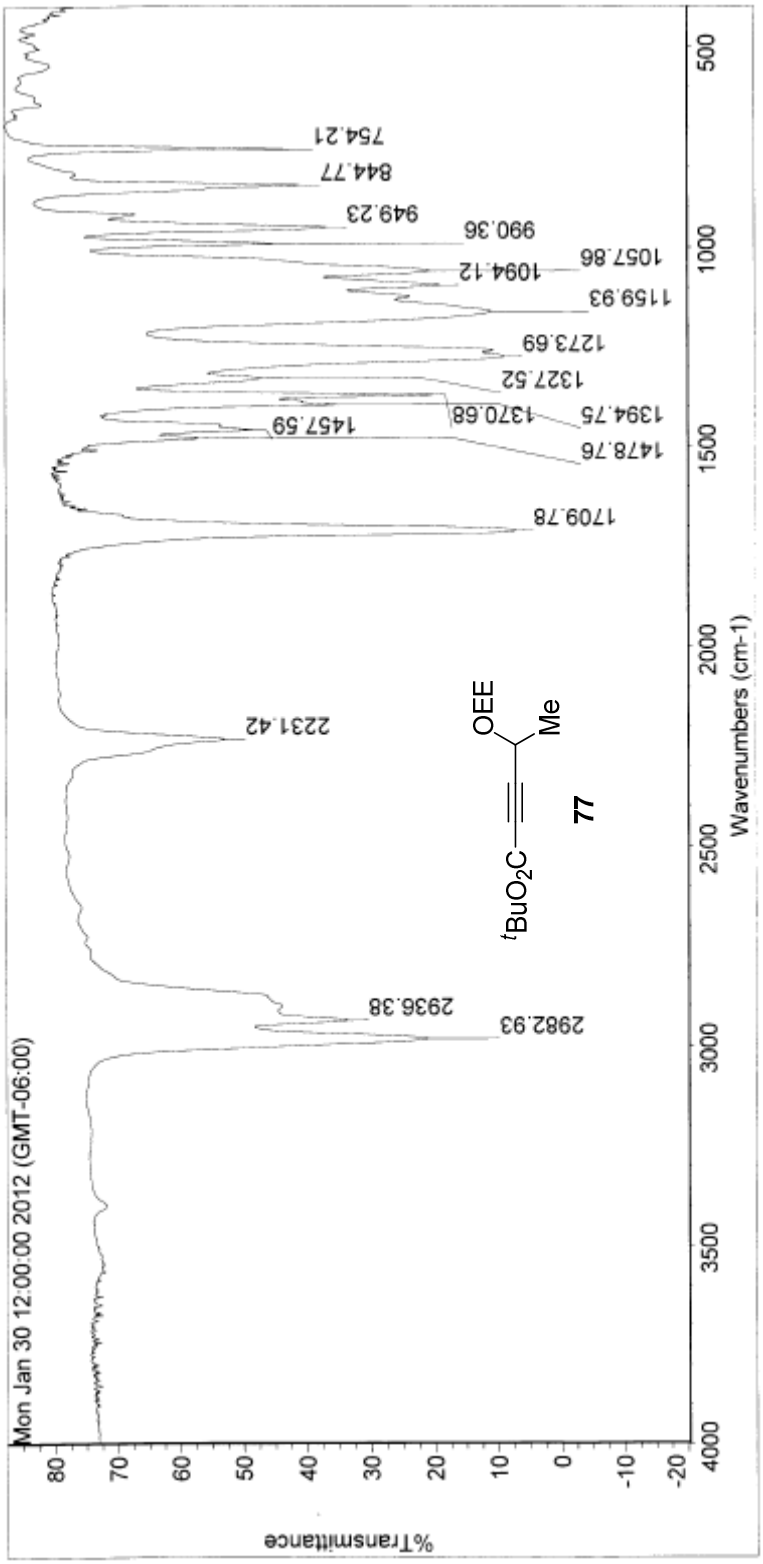
Pulse Sequence: s2pul

 Solvent: c6d6
 Ambient temperature
User:  1-14-87
File: ae_viii_97_s2pul_C13
INOVA-500  "nmrastro"

 Relax. delay 1.000 sec
 Pulse 30.0 degrees
 Acq. time 1.300 sec
 Width 24509.8 Hz
 512 repetitions
OBSERVE  C13, 100.5309491 MHz
DECOUPLE  H1, 399.8067465 MHz
 Power 44 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 42 sec
```



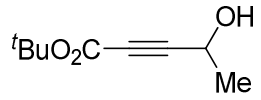
77


Mon Jan 30 12:00:00 2012 (GMT-06:00)
%Transmittance
Wavenumbers (cm-1)
2982.93
2936.38
2231.42
1709.78
1478.76
1457.59
1394.75
1370.68
1327.52
1273.69
1159.93
1094.12
1057.86
990.36
949.23
844.77
754.21
OEE
Me
$^{t}BuO_2C$
77

ae_viii_100p

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
25 repetitions
OBSERVE H1, 400.2669786 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 3 min, 44 sec



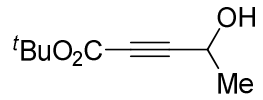
78

```
ae_viii_100p

 Archive directory:
 Sample directory:

Pulse Sequence: s2pul
 Solvent: c6d6
 Ambient temperature
User:  1-14-87
File: ae_viii_100p_s2pul_C13
INOVA-500  "nmrelroy"

 Relax. delay 1.000 sec
 Pulse 30.0 degrees
 Acq. time 1.300 sec
 Width 24509.8 Hz
 512 repetitions
OBSERVE  C13, 100.5309499 MHz
DECOUPLE  H1, 399.8067465 MHz
 Power 44 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 42 sec
```

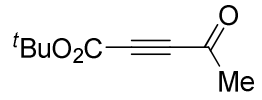


78

ae_viii_ketoester

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Mercury-400BB "nmr6"

 Relax. delay 2.000 sec
 Pulse 16.4 degrees
 Acq. time 2.856 sec
 Width 5602.2 Hz
 13 repetitions
OBSERVE   H1, 400.2669783 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 0 min, 0 sec



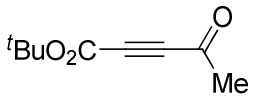
68

```
ae_viii_ketoester

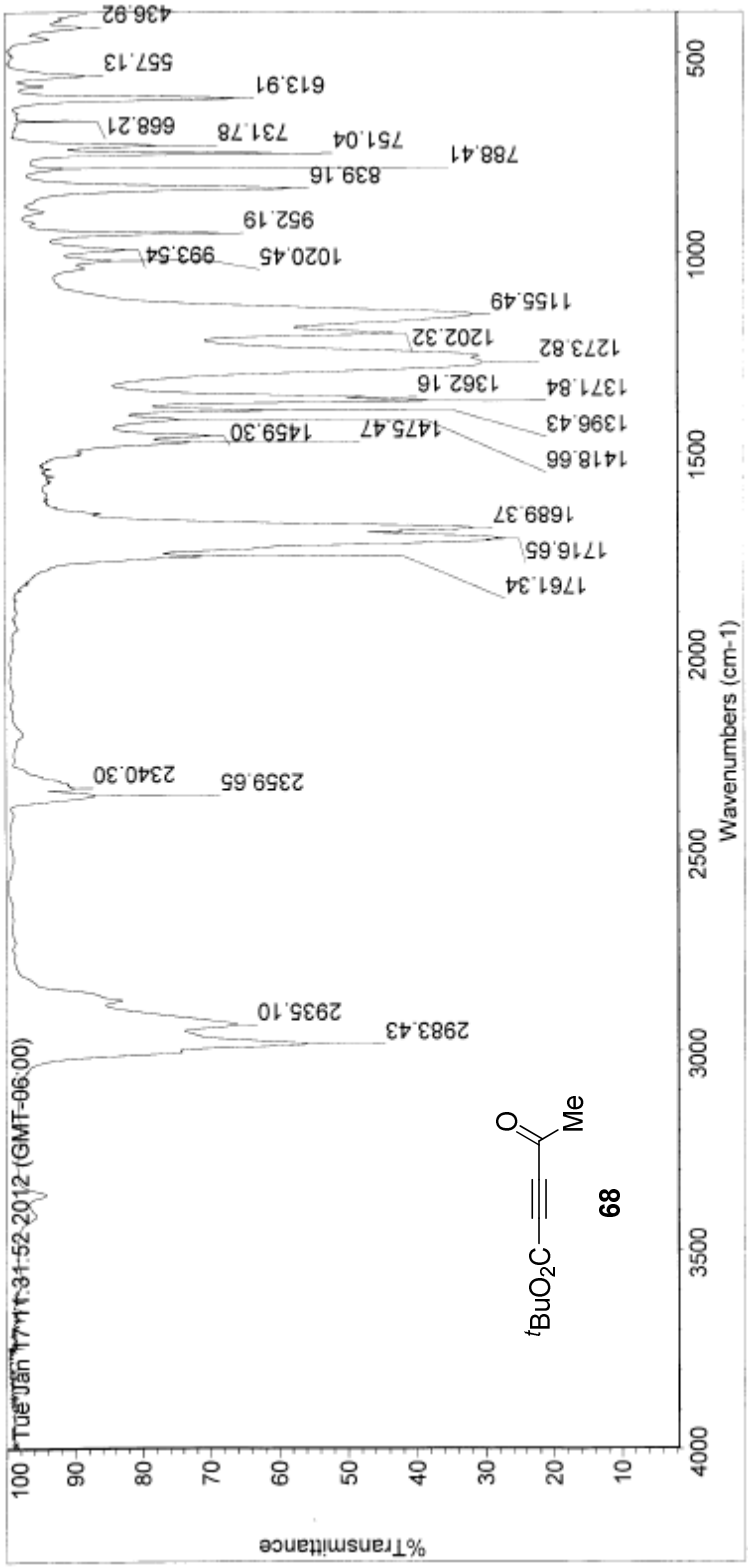
 Archive directory: /home/staff31/vnmrsys/data
 Sample directory: ae_viii_ketoester_20120117_01

Pulse Sequence: s2pul
 Solvent: cdcl3
 Temp. 25.0 C / 298.1 K
User:  1-14-87
File: CARBON_01
INOVA-500  "nmrfred"

 Relax. delay 2.000 sec
 Pulse 30.0 degrees
 Acq. time 1.285 sec
 Width 25510.2 Hz
 512 repetitions
OBSERVE  C13, 100.4987085 MHz
DECOUPLE  H1, 399.6783771 MHz
 Power 38 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 28 min, 6 sec
```



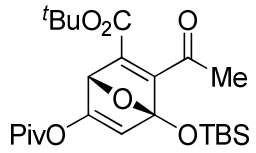
68


436.92
557.13
613.91
668.21
731.78
751.04
788.41
839.16
952.19
993.54
1020.45
1155.49
1202.32
1273.82
1362.16
1371.84
1396.43
1418.66
1459.30
1475.47
1689.37
1716.65
1761.34
2340.30
2359.65
2935.10
2983.43
Tue Jan 17 11:31:52 2012 (GMT-06:00)
%Transmittance
Wavenumbers (cm-1)
100
90
80
70
60
50
40
30
20
10
4000
3500
3000
2500
2000
1500
1000
500
O
Me
$^{t}BuO_2C$
68

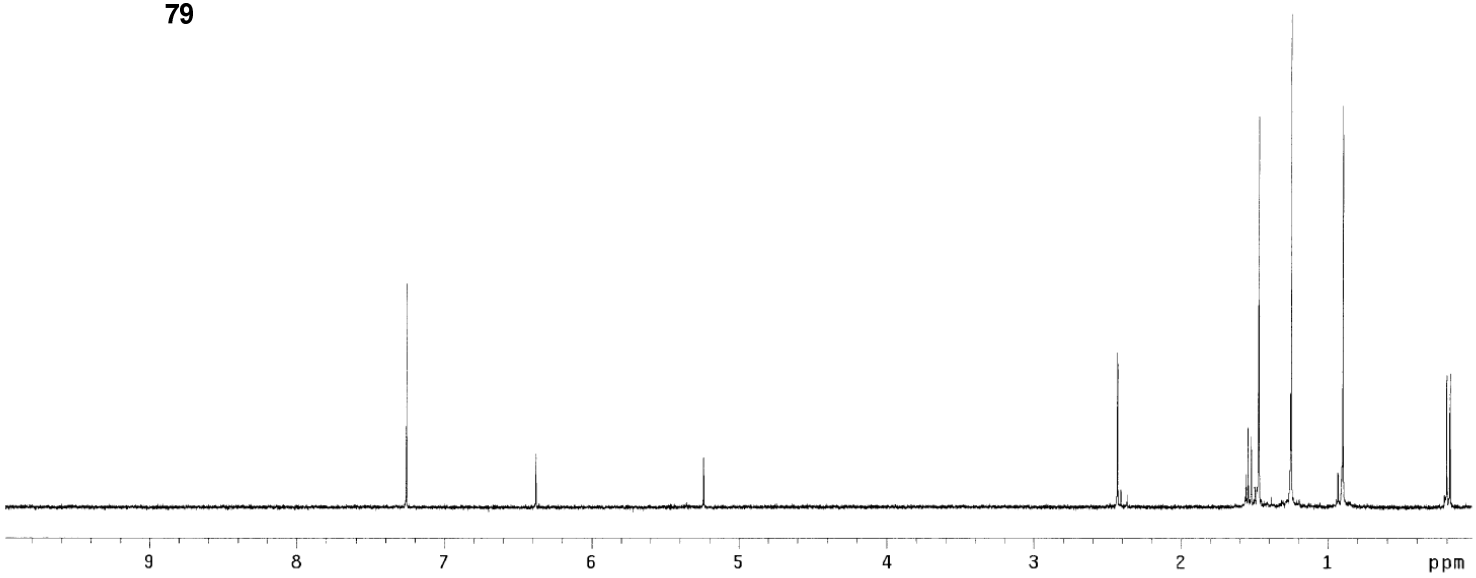
```
ae_ix_11

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Mercury-400BB  "nmr6"

 Relax. delay 2.000 sec
 Pulse 16.4 degrees
 Acq. time 2.856 sec
 Width 5602.2 Hz
 7 repetitions
OBSERVE   H1, 400.2669786 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 0 min, 0 sec
```



79



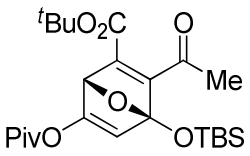
ae_ix_11

Archive directory:
Sample directory:

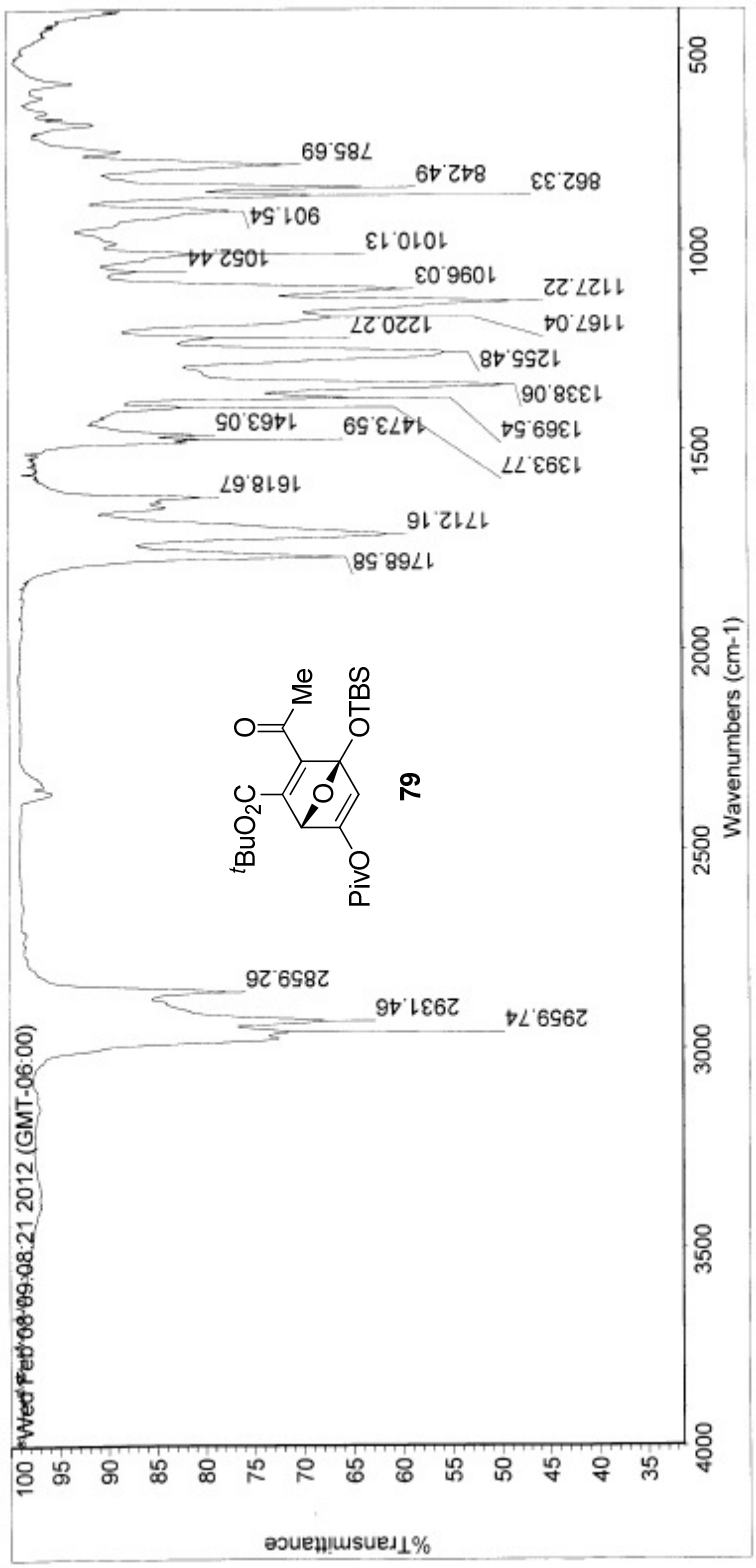
Pulse Sequence: s2pul

Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: ae_ix_11_s2pul_C13
INOVA-500 "nmrelroy"

Relax. delay 1.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
512 repetitions
OBSERVE C13, 100.5309756 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 42 sec



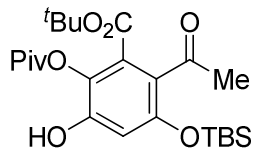
79


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
2959.74
2931.46
2859.26
1768.58
1712.16
1618.67
1393.77
1369.54
1473.59
1463.05
1338.06
1255.48
1220.27
1167.04
1127.22
1096.03
1052.44
1010.13
901.54
862.33
842.49
785.69
Me
O
OTBS
tBuO2C
O
PivO
79

```
ae_ix_10p2

Pulse Sequence: s2pul
 Solvent: CDCl3
 Ambient temperature
Mercury-400BB  "nmr6"

 Relax. delay 2.000 sec
 Pulse 16.4 degrees
 Acq. time 2.856 sec
 Width 5602.2 Hz
 15 repetitions
OBSERVE    H1, 400.2669783 MHz
DATA PROCESSING
 Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 52 sec
```



81

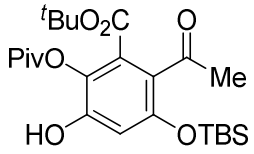
```
ae_ix_10

 Archive directory:
 Sample directory:

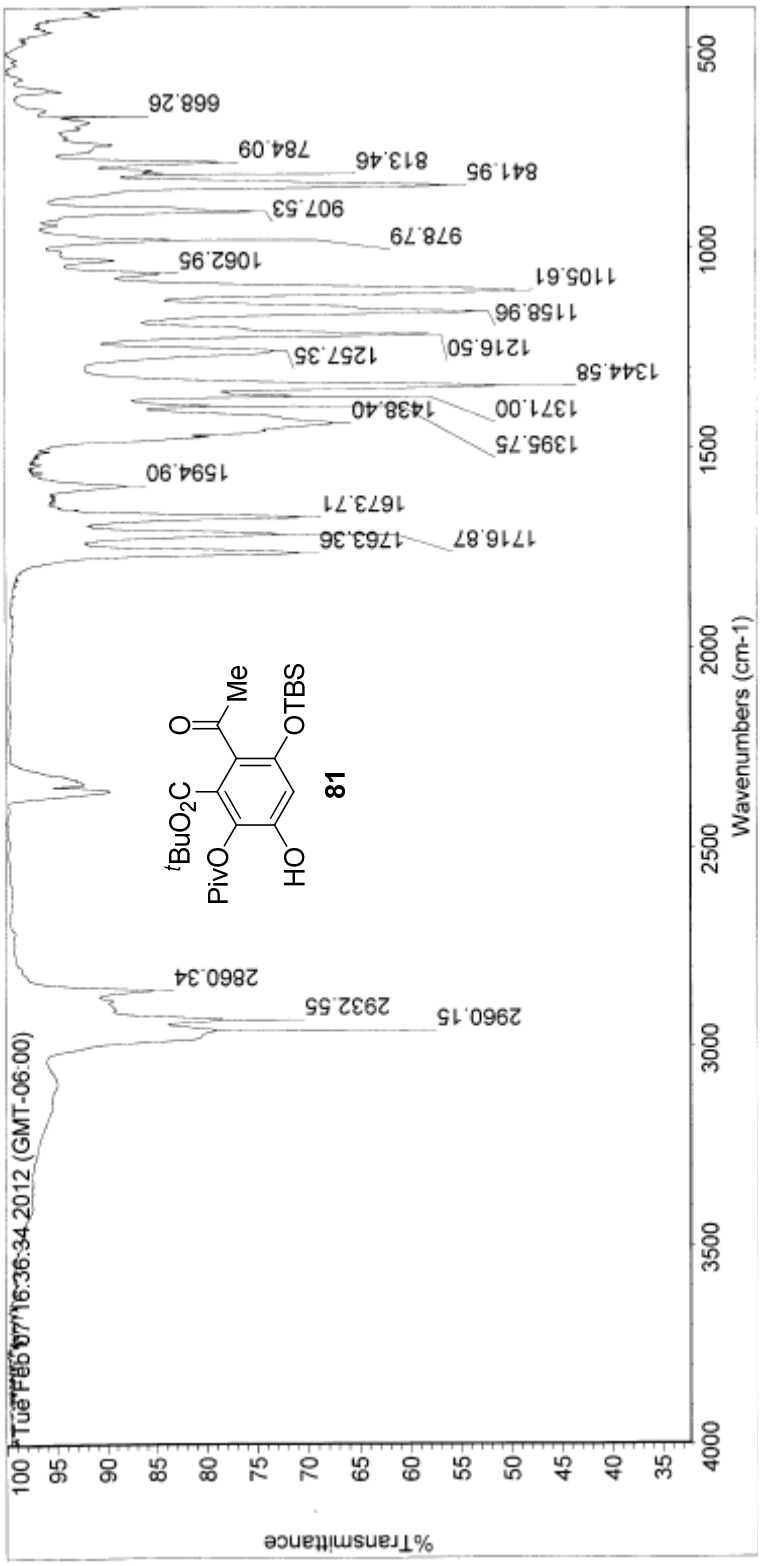
Pulse Sequence: s2pul

 Solvent: cdcl3
 Ambient temperature
User:  1-14-87
File: ae_ix_10_s2pul_C13
INOVA-500  "nmrelroy"

 Relax. delay 1.000 sec
 Pulse 30.0 degrees
 Acq. time 1.300 sec
 Width 24509.8 Hz
 512 repetitions
OBSERVE  C13, 100.5309756 MHz
DECOUPLE  H1, 399.8067105 MHz
 Power 44 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 2.0 Hz
FT size 65536
Total time 19 min, 42 sec
```



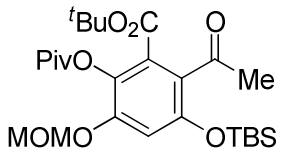
81


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
2960.15
2932.55
2860.34
1716.87
1763.36
1673.71
1594.90
1395.75
1371.00
1438.40
1344.58
1257.35
1216.50
1158.96
1105.61
1062.95
978.79
907.53
841.95
813.46
784.09
668.26
Me
O
OTBS
^{t}BuO$_2$C
PivO
HO
81

ae_viii_105

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
16 repetitions
OBSERVE H1, 400.2669779 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 52 sec

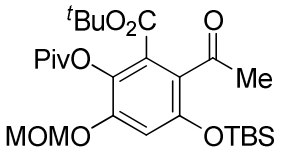


83

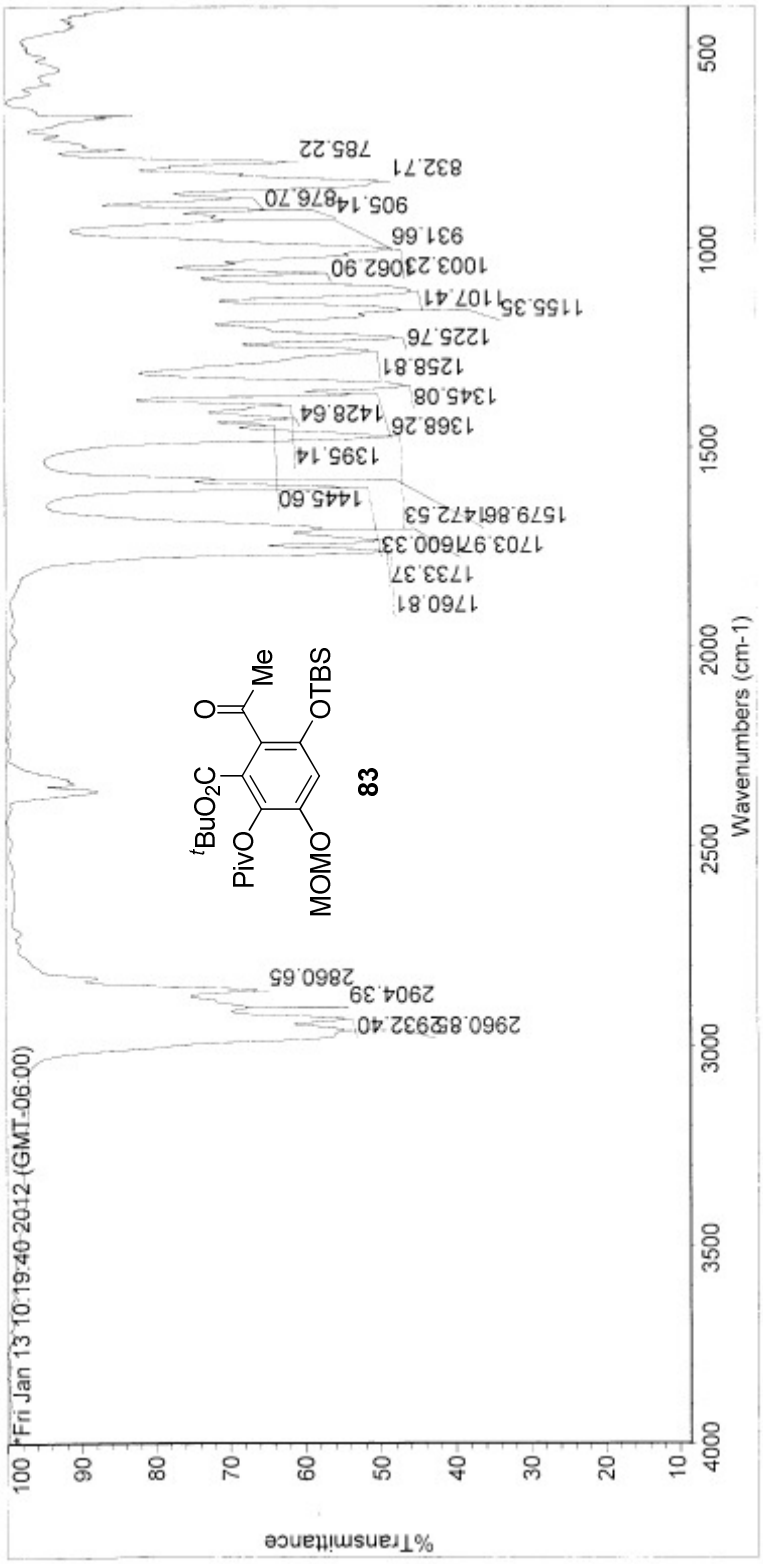
13C OBSERVE

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

Relax. delay 2.000 sec
Pulse 22.5 degrees
Acq. time 1.280 sec
Width 25188.9 Hz
64 repetitions
OBSERVE C13, 100.6472177 MHz
DECOUPLE H1, 400.2689955 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 7 min, 49 sec



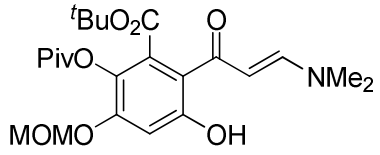
83


Fri Jan 13 10:19:40 2012 (GMT-06:00)
%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
90
80
70
60
50
40
30
20
10
2960.85
2932.40
2904.39
2860.65
1760.81
1733.37
1703.97
1600.33
1579.86
1472.53
1445.60
1395.14
1368.26
1428.64
1345.08
1258.81
1225.76
1155.35
1107.41
1062.90
1003.23
931.66
905.14
876.70
832.71
785.22
OTBS
Me
O
^{t}BuO$_2$C
PivO
MOMO
83

enamenone

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 10000.0 Hz
12 repetitions
OBSERVE H1, 400.2669782 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 2 min, 15 sec

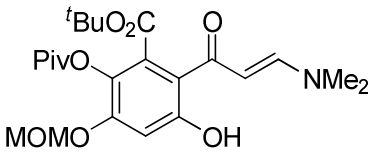


93

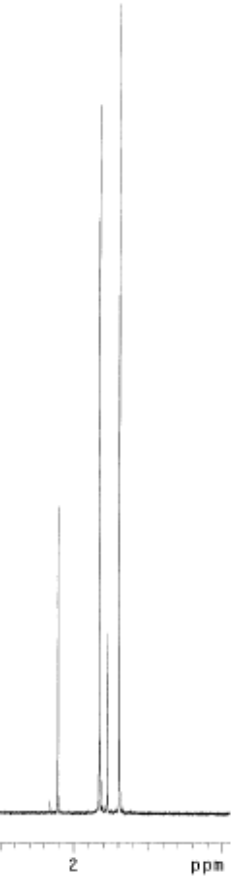
13C OBSERVE

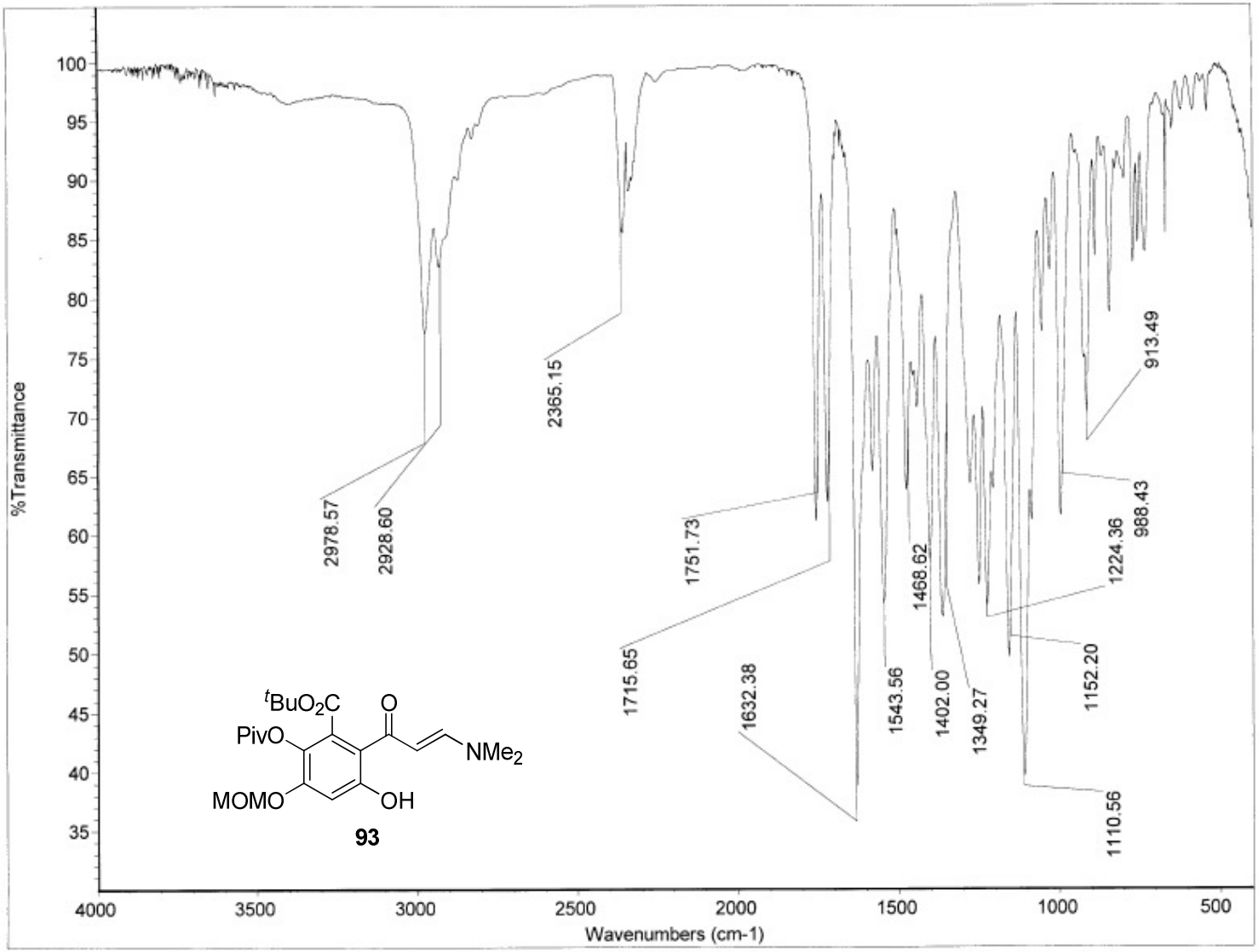
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

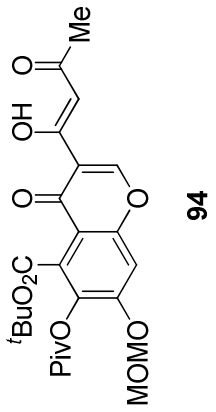
Relax. delay 2.000 sec
Pulse 22.5 degrees
Acq. time 1.280 sec
Width 25188.9 Hz
141 repetitions
OBSERVE C13, 100.6472307 MHz
DECOUPLE H1, 400.2689955 MHz
Power 38 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 1.0 Hz
FT size 65536
Total time 0 min, 0 sec



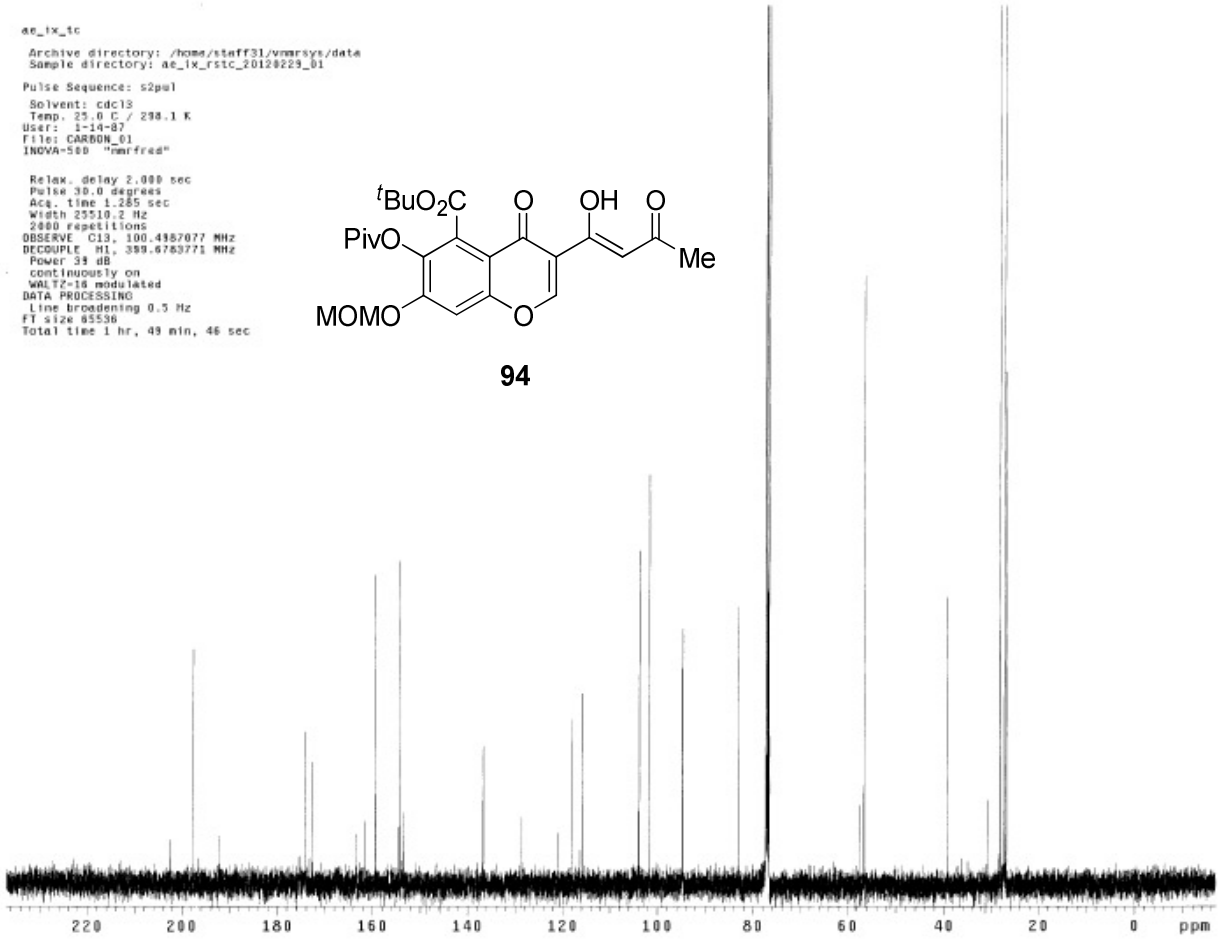
93

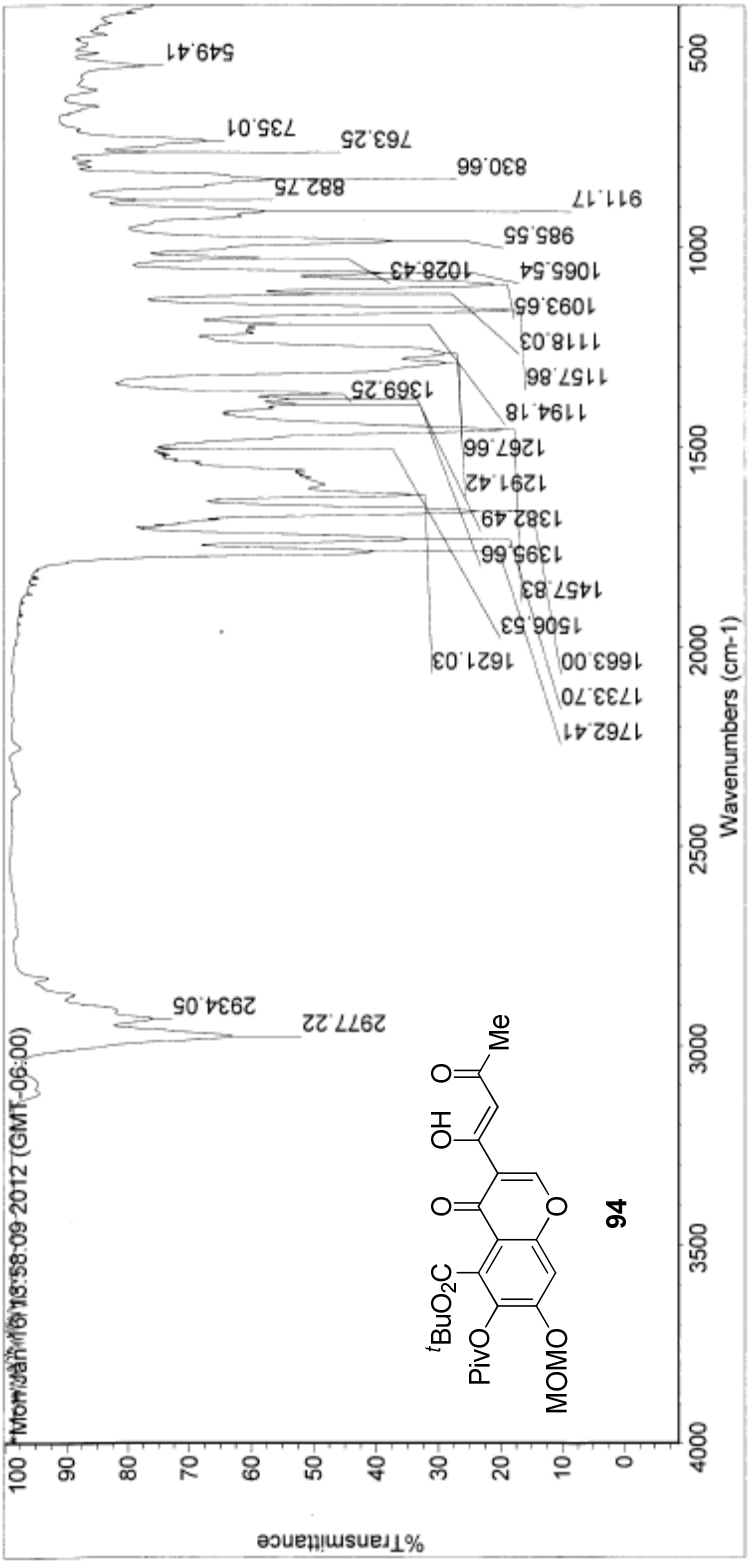

2
ppm

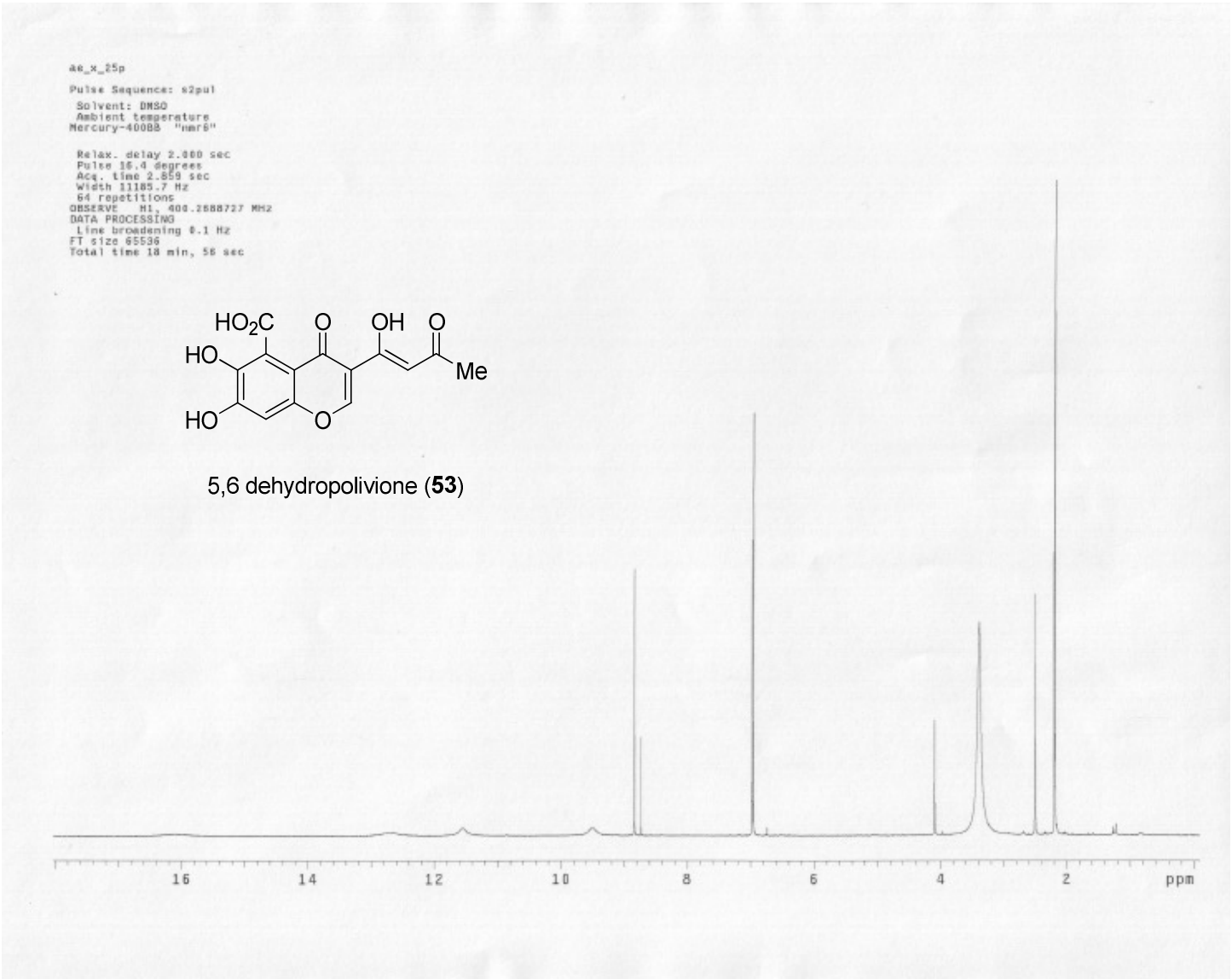

%Transmittance
100
95
90
85
80
75
70
65
60
55
50
45
40
35
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)
2978.57
2928.60
2365.15
1751.73
1715.65
1632.38
1543.56
1468.62
1402.00
1349.27
1224.36
1152.20
1110.56
988.43
913.49
tBuO2C
O
PivO
NMe2
MOMO
OH
93



94


ae_ix_tc
Archive directory: /home/staff31/vnmrsys/data
Sample directory: ae_ix_rstc_20120229_01
Pulse Sequence: s2pul
Solvent: cdcl3
Temp. 25.0 C / 298.1 K
User: 1-14-87
File: CARBON_01
INOVA-500 "nmrfred"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.285 sec
Width 25510.2 Hz
2000 repetitions
OBSERVE C13, 100.4987077 MHz
DECOUPLE H1, 399.6783771 MHz
Power 39 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 65536
Total time 1 hr, 49 min, 46 sec
tBuO2C
O
OH
O
PivO
Me
MOMO
O
94
220
200
180
160
140
120
100
80
60
40
20
0
ppm


%Transmittance
Wavenumbers (cm-1)
549.41
735.01
763.25
830.66
882.75
911.17
985.55
1065.54
1028.43
1093.65
1118.03
1157.86
1369.25
1194.18
1267.66
1291.42
1382.49
1395.66
1457.83
1506.53
1621.03
1663.00
1733.70
1762.41
2934.05
2977.22
OH
O
Me
O
O
^{t}BuO$_2$C
PivO
MOMO
94



5,6 dehydropolivione (**53**)

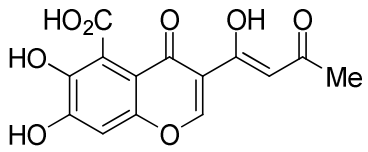
```
ae_x_24p2

 Archive directory: /home/staff31/vnmrsys/data
 Sample directory: ae_x_24p2_20120503_01

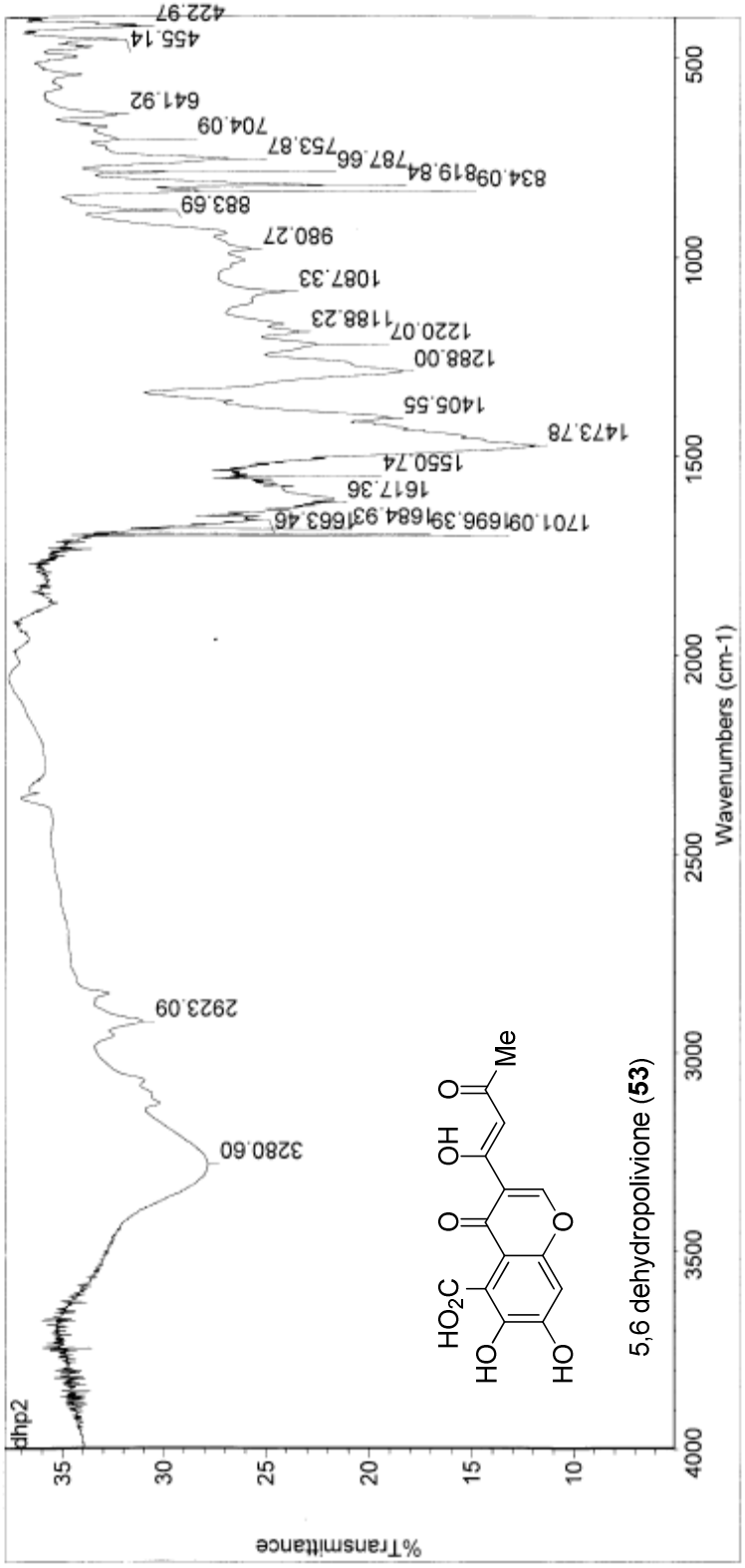
Pulse Sequence: s2pul

 Solvent: dmsO
 Temp. 25.0 C / 298.1 K
User:  1=14=87
File: CARBON_01
INOVA-500  "nmrfred"

 Relax. delay 1.000 sec
 Pulse 30.0 degrees
 Acq. time 1.311 sec
 Width 25000.0 Hz
 5008 repetitions
OBSERVE   C13, 100.4990579 MHz
DECOUPLE  H1, 399.6796241 MHz
 Power 39 dB
 continuously on
 WALTZ-16 modulated
DATA PROCESSING
 Line broadening 0.5 Hz
FT size 65536
Total time 3 hr, 13 min, 17 sec
```



5,6 dehydropolivione (**53**)



5,6 dehydropolivione (**53**)

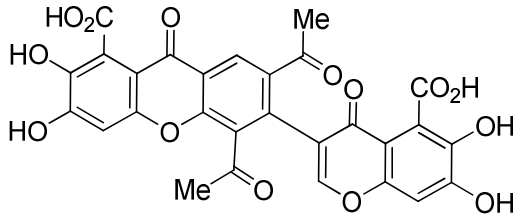
Me
O
O
CO2H
OH
OH
O
O
Me
O
O
HO2C
HO
HO
vinaxanthone (1)
ppm
1
2
3
4
5
6
7
8
9
10
11
12
13

500 MHz nmr0

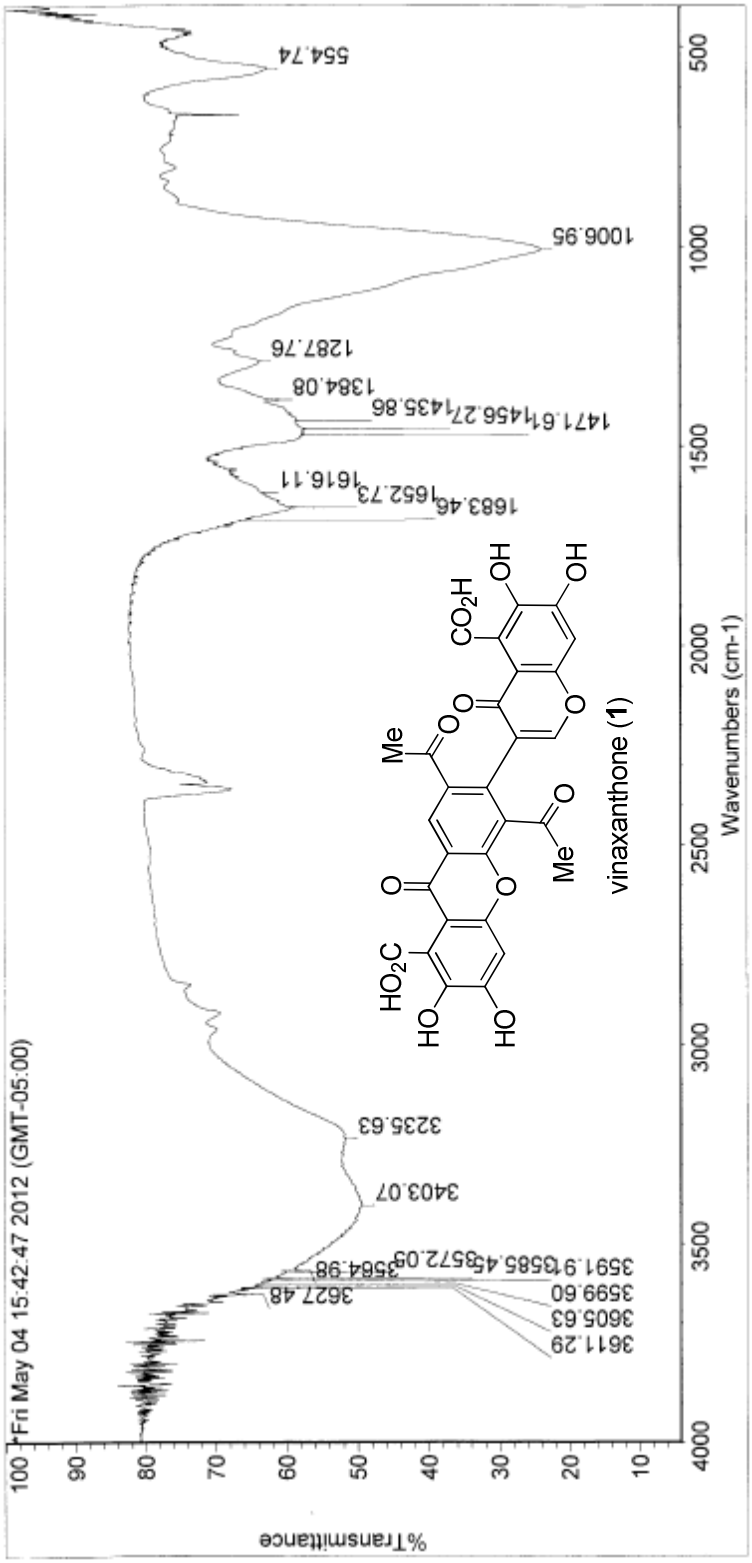
vinaxanthone_d6_dmso_c13

exp4 Carbon

SAMPLE		SPECIAL	
date	May 3 2012	temp	27.0
solvent	dmso	gain	50
file	exp	spin	20
ACQUISITION		hst	0.008
sw	30165.9	pw90	9.500
at	2.000	alfa	10.000
np	120664	FLAGS	
fb	17000	il	n
bs	8	in	n
d1	2.000	dp	y
nt	15000	hs	nn
ct	12625	PROCESSING	
TRANSMITTER		lb	2.00
tn	C13	fn	not used
sfrq	125.705	DISPLAY	
tof	1255.4	sp	-628.7
tpwr	53	wp	28280.5
pw	9.500	rfl	6939.9
DECOUPLER		rfp	4964.8
dn	H1	rp	-86.4
dof	0	lp	-251.5
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	37	sc	0
dmf	10582	vs	42822
		th	17
		ai	ph



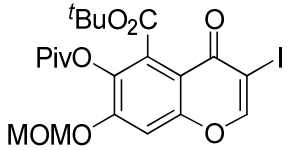
vinaxanthone (**1**)


Fri May 04 15:42:47 2012 (GMT-05:00)
%Transmittance
Wavenumbers (cm-1)
vinaxanthone (1)
554.74
1006.95
1287.76
1384.08
1435.86
1456.27
1471.61
1616.11
1652.73
1683.46
3235.63
3403.07
3564.98
3572.03
3585.45
3591.97
3599.60
3605.63
3611.29
3627.48

ae_viii_77p1

Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"

Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
16 repetitions
OBSERVE H1, 400.2669786 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 1 min, 52 sec



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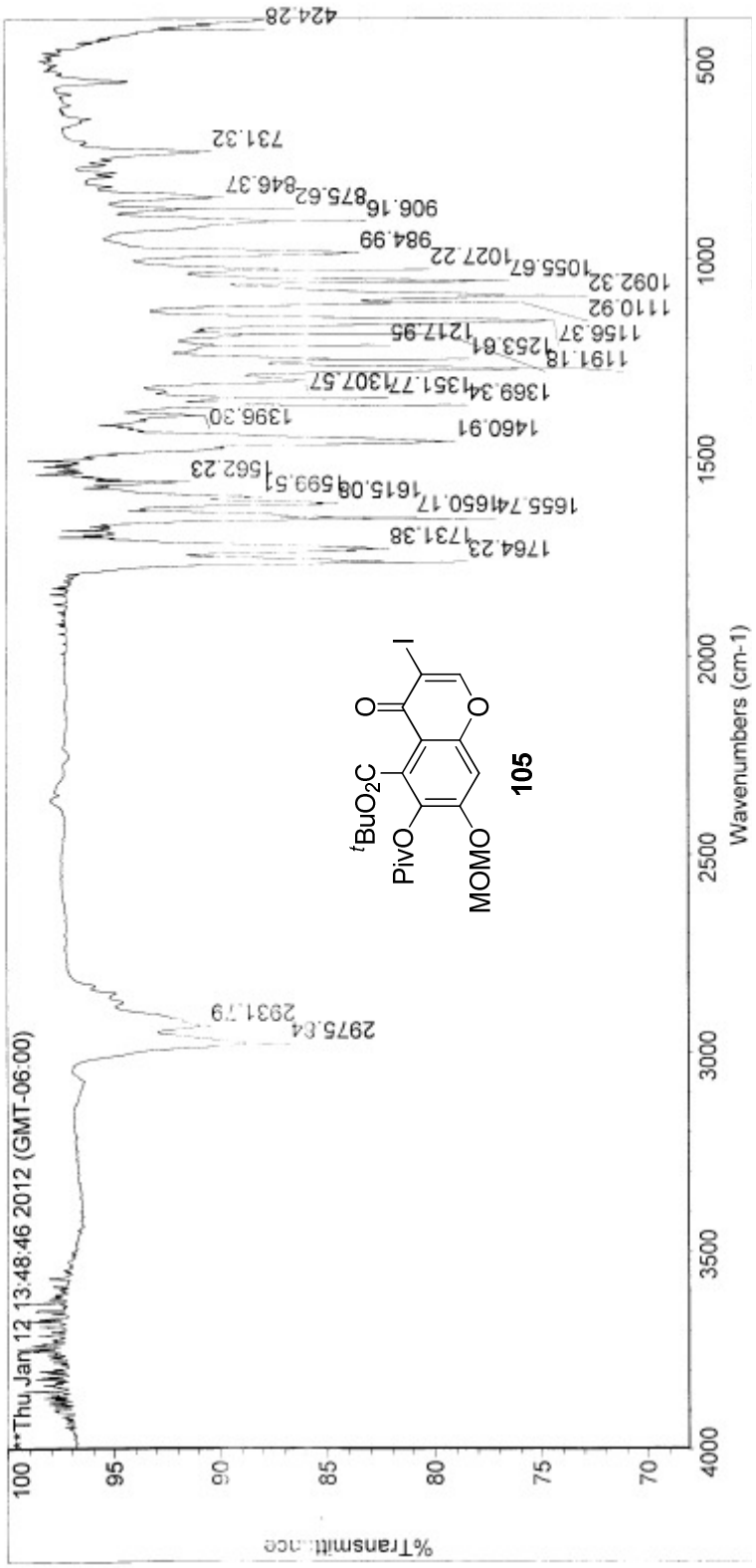
ae_ix_I
Archive directory:
Sample directory:
Pulse Sequence: s2pul
Solvent: cdcl3
Ambient temperature
User: 1-14-87
File: ae_ix_I2_s2pul_C13
INOVA-500 "nmrelroy"
Relax. delay 2.000 sec
Pulse 30.0 degrees
Acq. time 1.300 sec
Width 24509.8 Hz
1000 repetitions
OBSERVE C13, 100.5309747 MHz
DECOUPLE H1, 399.8067105 MHz
Power 44 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 2.0 Hz
FT size 65536
Total time 55 min, 9 sec
tBuO2C
PivO
MOMO
O
I
O
105
180
160
140
120
100
80
60
40
20
ppm

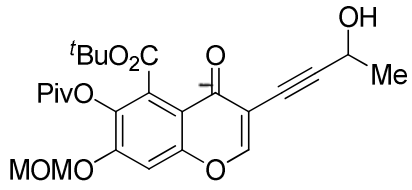

%Transmittance
Wavenumbers (cm-1)
Thu Jan 12 13:48:46 2012 (GMT-06:00)
2975.64
2931.79
1764.23
1731.38
1655.74
1650.17
1615.08
1599.51
1562.23
1460.91
1396.30
1369.34
1351.77
1307.57
1191.18
1253.81
1217.95
1156.37
1110.92
1092.32
1055.67
1027.22
984.99
906.16
875.62
846.37
731.32
424.28
I
O
O
^{t}BuO$_2$C
PivO
MOMO

105

```
ynol

exp1  PROTON

      SAMPLE                PRESATURATION
date   Jan 17 2012  satmode            n
solvent      cdcl3  wet                n
file /mnt/nhbrobo/~       SPECIAL
mrc_tbuynol_201201~ temp           25.0
17_01/PROTON_01,fi~ gain             30
                 d  spin             20
   ACQUISITION      hst           0.008
sw          6410.3  pw90          6.900
at           2.556  alfa         10.000
np           32768       FLAGS
fb            4000  il                 n
bs              32  in                 n
d1           2.000  dp                 y
nt              16  hs                nn
ct              16      PROCESSING
   TRANSMITTER       fn         not used
tn              H1       DISPLAY
sfrq       399.679  sp               1.3
tof          399.7  wp            3987.2
tpwr            62  rf1           3708.3
pw           2.300  rfp           2901.7
    DECOUPLER       rp             -17.0
dn             C13  lp              -7.7
dof              0       PLOT
dm             nnn  wc               250
decwave W40_OneNMR~ sc                 0
              _W011  vs                57
dpwr             36  th                 1
dmf           29412  al  cdc  ph
```



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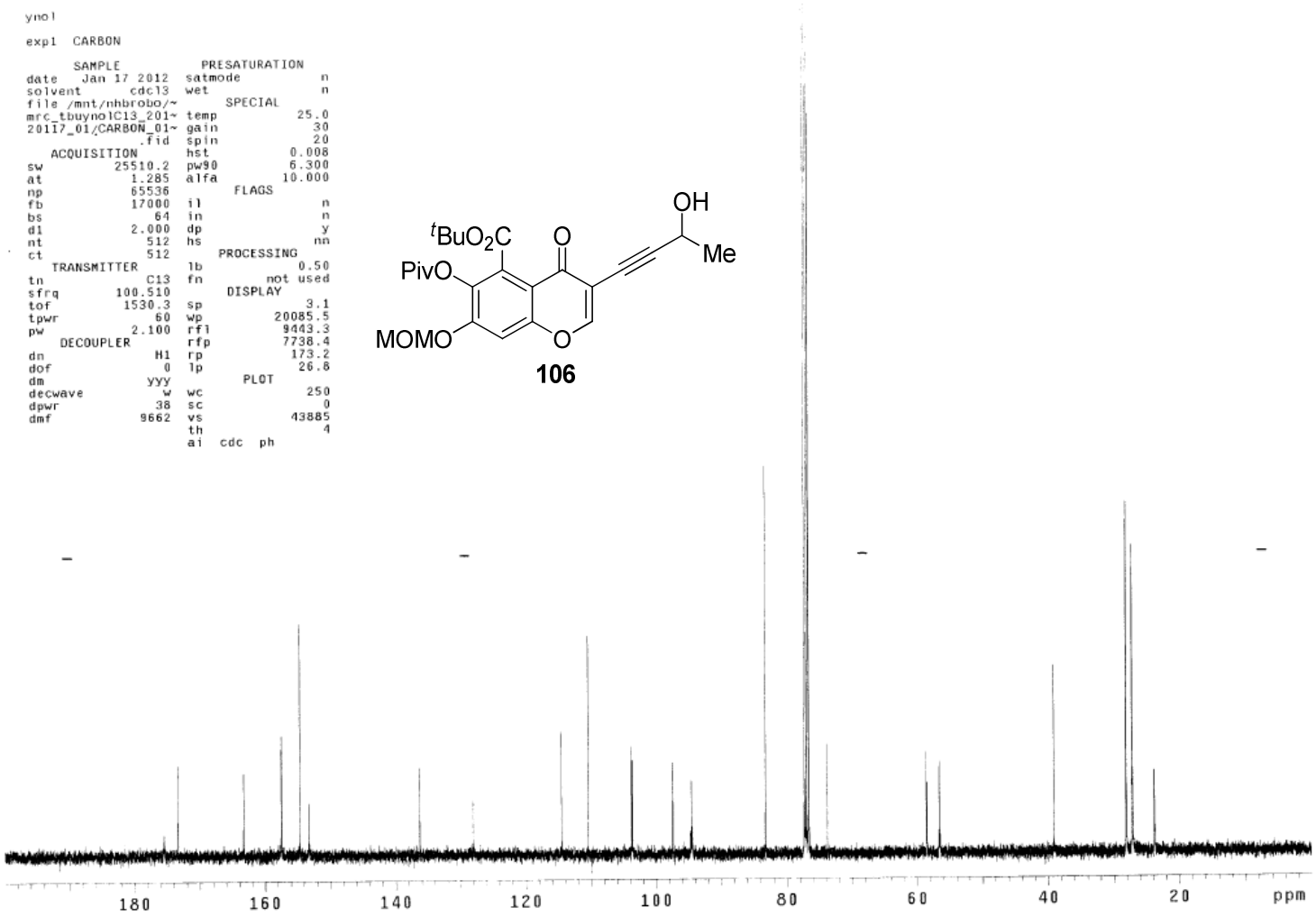
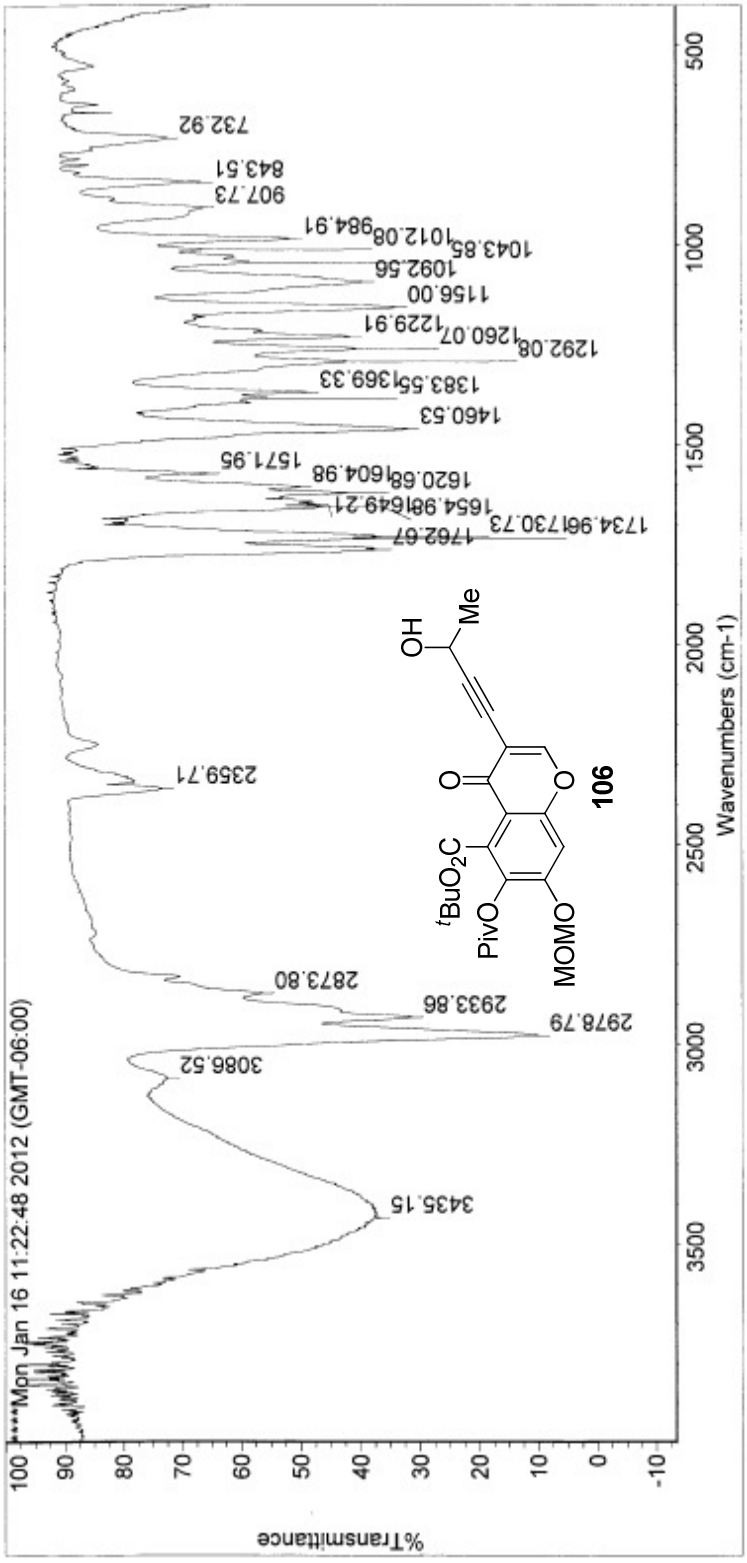
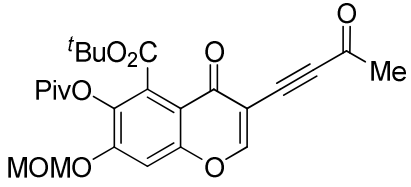

ynol
expl CARBON
SAMPLE
date Jan 17 2012
solvent cdcl3
file /mnt/nhbrobo/~
mrc_tbuynolC13_201~
20117_01/CARBON_01~
.fid
ACQUISITION
sw 25510.2
at 1.285
np 65536
fb 17000
bs 64
d1 2.000
nt 512
ct 512
TRANSMITTER
tn C13
sfrq 100.510
tof 1530.3
tpwr 60
pw 2.100
DECOUPLER
dn H1
dof 0
dm yyy
decwave w
dpwr 38
dmf 9662
PRESATURATION
satmode n
wet n
SPECIAL
temp 25.0
gain 30
spin 20
hst 0.008
pw90 6.300
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp 3.1
wp 20085.5
rfl 9443.3
rfp 7738.4
rp 173.2
lp 26.8
PLOT
wc 250
sc 0
vs 43885
th 4
ai cdc ph
tBuO2C
O
OH
PivO
Me
MOMO
O
106
180
160
140
120
100
80
60
40
20
ppm


%Transmittance
Wavenumbers (cm-1)
****Mon Jan 16 11:22:48 2012 (GMT-06:00)
3435.15
3086.52
2978.79
2933.86
2873.80
2359.71
1762.67
1734.96
1730.73
1654.98
1649.21
1620.68
1604.98
1571.95
1460.53
1383.55
1369.33
1292.08
1260.07
1229.91
1156.00
1092.56
1043.85
1012.08
984.91
907.73
843.51
732.92
106
OH
Me
O
O
PivO
MOMO
tBuO2C

ynone

exp1 PROTON

SAMPLE		PRESATURATION	
date	Jan 13 2012	satmode	n
solvent	cdcl3	wet	n
file	/mnt/nhbrobo/~	SPECIAL	
mrc_tbuynone_20120~		temp	25.0
113_02/PROTON_01.f~		gain	30
	id	spin	20
ACQUISITION		hst	0.008
sw	6410.3	pw90	6.900
at	2.556	alfa	10.000
np	32768	FLAGS	
fb	4000	il	n
bs	32	in	n
d1	2.000	dp	y
nt	16	hs	nn
ct	16	PROCESSING	
TRANSMITTER		fn	not used
tn	H1	DISPLAY	
sfrq	399.679	sp	1.3
tof	399.7	wp	3995.5
tpwr	62	rfl	3708.3
pw	2.300	rfp	2901.7
DECOUPLER		rp	28.8
dn	C13	lp	1.8
dof	0	PLOT	
dm	nnn	wc	250
decwave	W40_OneNMR~	sc	0
	_W011	vs	101
dpwr	36	th	11
dmf	29412	ai cdc ph	



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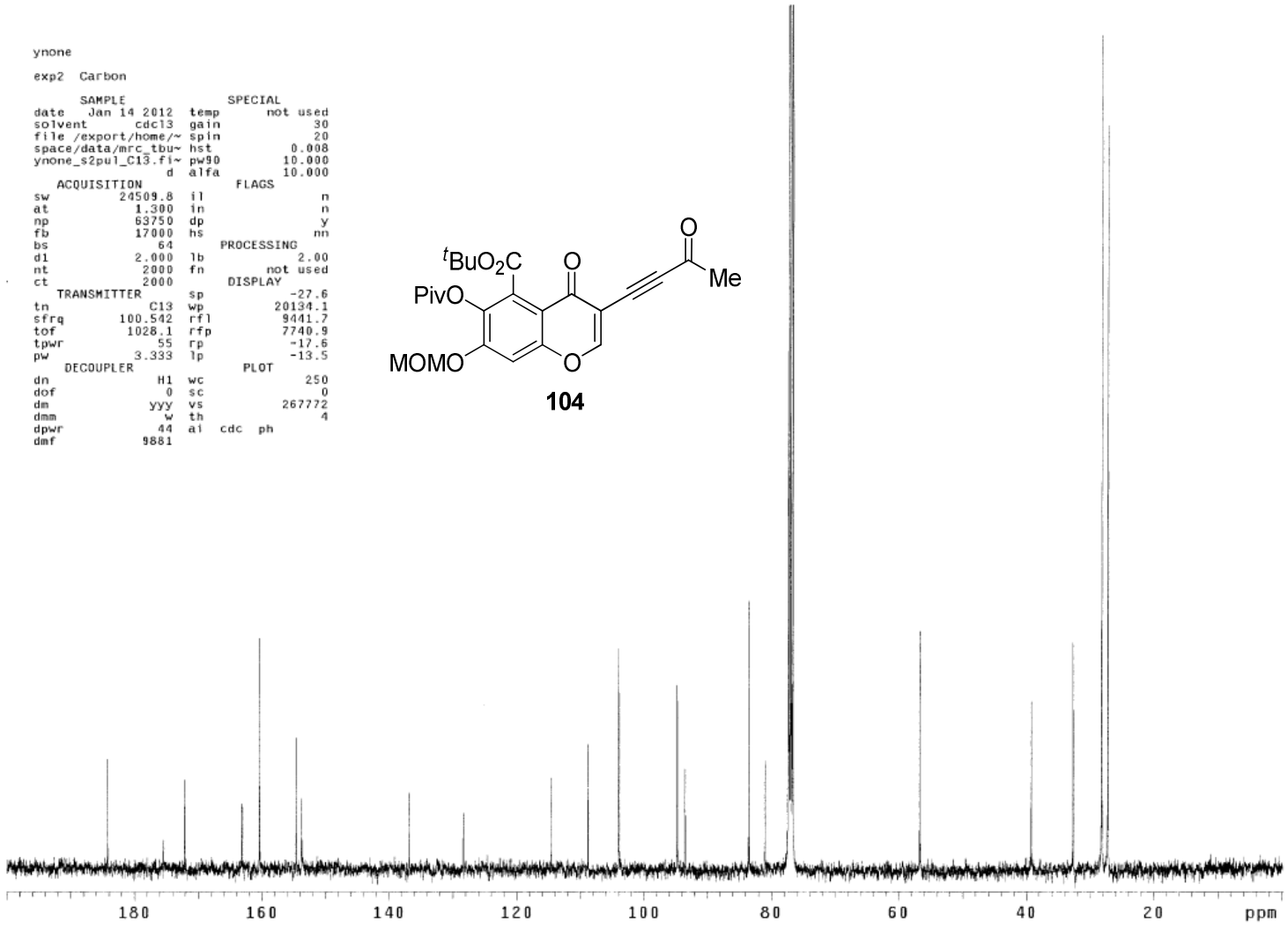
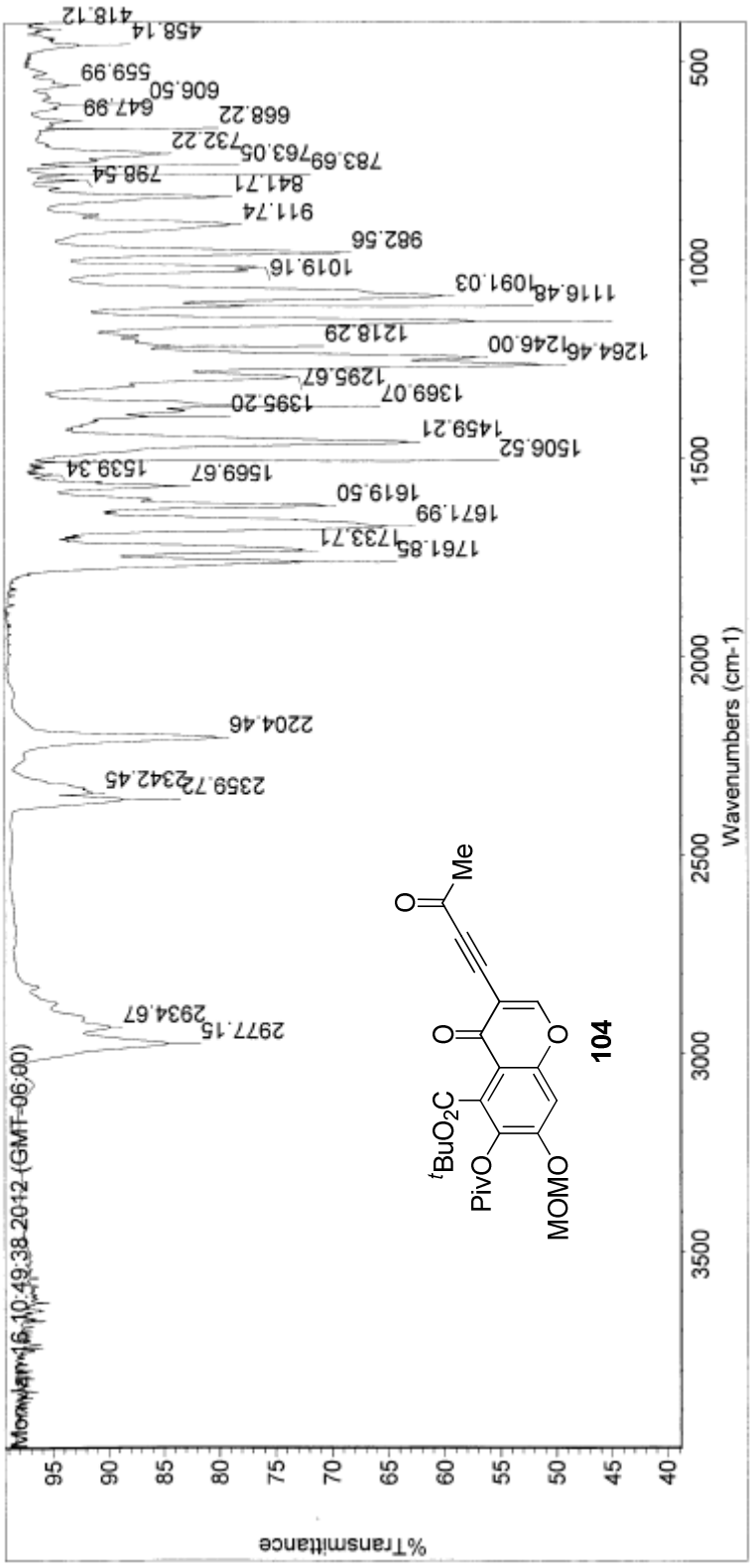
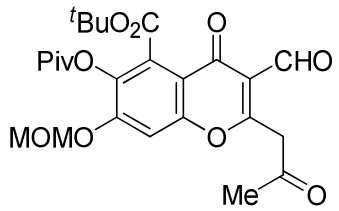

ynone
exp2 Carbon
SAMPLE
date Jan 14 2012
solvent cdcl3
file /export/home/~
space/data/mrc_tbu~
ynone_s2pul_C13.fi~
d
ACQUISITION
sw 24509.8
at 1.300
np 63750
fb 17000
bs 64
d1 2.000
nt 2000
ct 2000
TRANSMITTER
tn C13
sfrq 100.542
tof 1028.1
tpwr 55
pw 3.333
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 44
dmf 9881
SPECIAL
temp not used
gain 30
spin 20
hst 0.008
pw90 10.000
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 2.00
fn not used
DISPLAY
sp -27.6
wp 20134.1
rfl 9441.7
rfp 7740.9
rp -17.6
lp -13.5
PLOT
wc 250
sc 0
vs 267772
th 4
al cdc ph
tBuO2C
PivO
MOMO
O
Me
104
180
160
140
120
100
80
60
40
20
ppm


%Transmittance
Wavenumbers (cm-1)
95
90
85
80
75
70
65
60
55
50
45
40
3500
3000
2500
2000
1500
1000
500
2977.15
2934.67
2359.72
2342.45
2204.46
1761.85
1733.71
1671.99
1619.50
1569.67
1539.34
1506.52
1459.21
1395.20
1369.07
1295.67
1264.46
1246.00
1218.29
1116.48
1091.03
1019.16
982.56
911.74
841.71
798.54
783.69
763.05
732.22
668.22
647.99
606.50
559.99
458.14
418.12
Me
O
O
O
O
^{t}BuO$_2$C
PivO
MOMO
104

aldehyde

exp1 std1h

SAMPLE		DEC. & VT	
date	Feb 9 2012	dfrq	400.269
solvent	CDCl3	dn	H1
file	exp	dpwr	30
ACQUISITION		dof	0
sfrq	400.269	dm	nnn
tn	H1	dmm	c
at	2.856	dmf	200
np	32000	PROCESSING	
sw	5602.2	lb	0.10
fb	not used	wtfile	
bs	1	proc	ft
tpwr	58	fn	not used
pw	2.0		
d1	2.000	werr	
tof	169.9	wexp	
nt	32	wbs	
ct	32	wnt	
alock	n		
gain	not used		
FLAGS			
il	n		
in	n		
dp	y		
DISPLAY			
sp	-3.2		
wp	4807.9		
vs	151		
sc	0		
wc	250		
hzmm	19.23		
is	1820.89		
rfl	3519.5		
rfp	2905.9		
th	14		
ins	100.000		
nm cdc ph			



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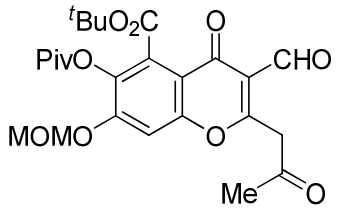
500 MHz nmr0

mom_piv_bu_aldehyde

exp4 Carbon

SAMPLE		SPECIAL	
date	Feb 20 2012	temp	27.0
solvent	cdcl3	gain	50
file	exp	spin	20
ACQUISITION		hst	0.008
sw	32679.7	pw90	9.500
at	1.958	alfa	10.000
np	128000	FLAGS	
fb	18000	il	n
bs	16	in	n
d1	2.000	dp	y
nt	13000	hs	nn
ct	13000	PROCESSING	
TRANSMITTER		lb	2.00
tn	C13	fn	not used
sfrq	125.705	DISPLAY	
tof	1883.9	sp	-628.5
tpwr	53	wp	28280.1
pw	3.163	rfl	12222.5
DECOUPLER		rfp	9678.2
dn	H1	rp	-96.8
dof	0	lp	-236.3
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	37	sc	0
dmf	10582	vs	8330
		th	9
		ai cdc ph	



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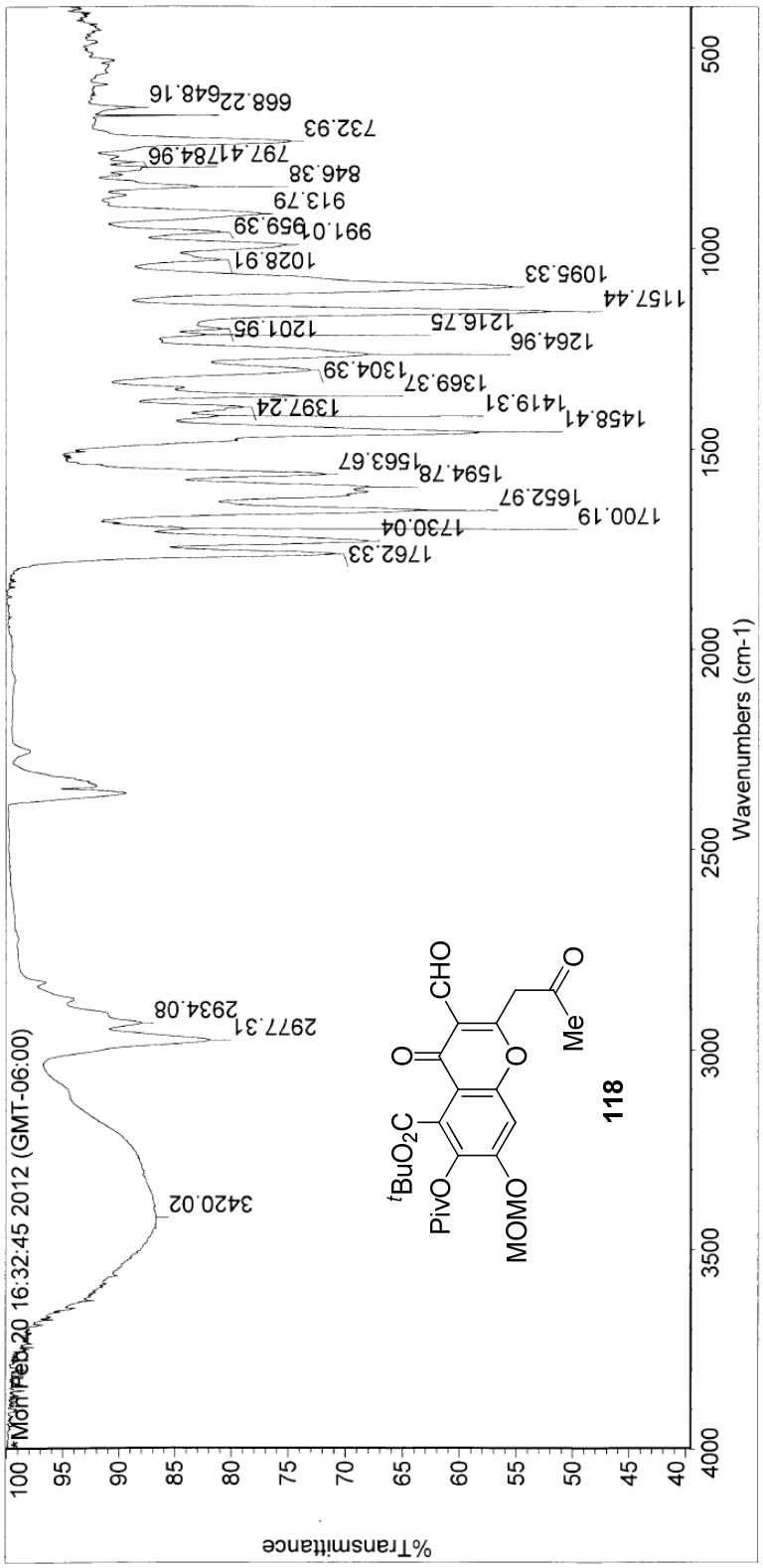
%Transmittance
Wavenumbers (cm-1)
Mon Feb 20 16:32:45 2012 (GMT-06:00)
3420.02
2977.31
2934.08
1762.33
1730.04
1700.19
1652.97
1594.78
1563.67
1458.41
1419.31
1397.24
1369.37
1304.39
1264.96
1216.75
1201.95
1157.44
1095.33
1028.91
991.07
959.39
913.79
846.38
797.41
784.96
732.93
668.22
648.16
PivO
MOMO
Me
O
CHO
118

```
mrc_aldehydedmadc6d6

exp1  PROTON

      SAMPLE              PRESATURATION
date   Feb 21 2012  satmode           n
solvent       c6d6  wet               n
file /mnt/nhbrobo/~       SPECIAL
mrc_aldehydedmadc6~ temp          25.0
d6_20120221_01/PRO~ gain            30
        TON_01.fid  spin            20
   ACQUISITION      hst          0.008
sw          6410.3  pw90         6.800
at           2.556  alfa        10.000
np           32768        FLAGS
fb            4000  il                n
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ct              32       PROCESSING
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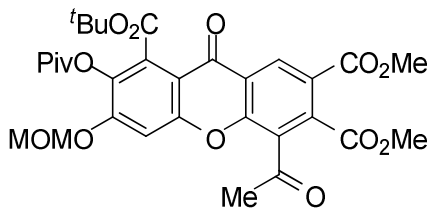

122

aldehydedmad_cyclization

exp1 CARBON

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	01.fid	spin	20
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at	1.285	alfa	10.000
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d1	2.000	dp	y
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ct	512	PROCESSING	
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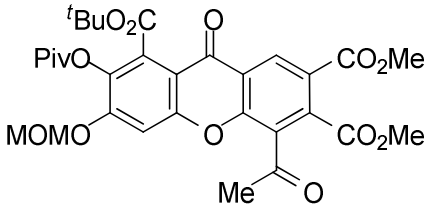
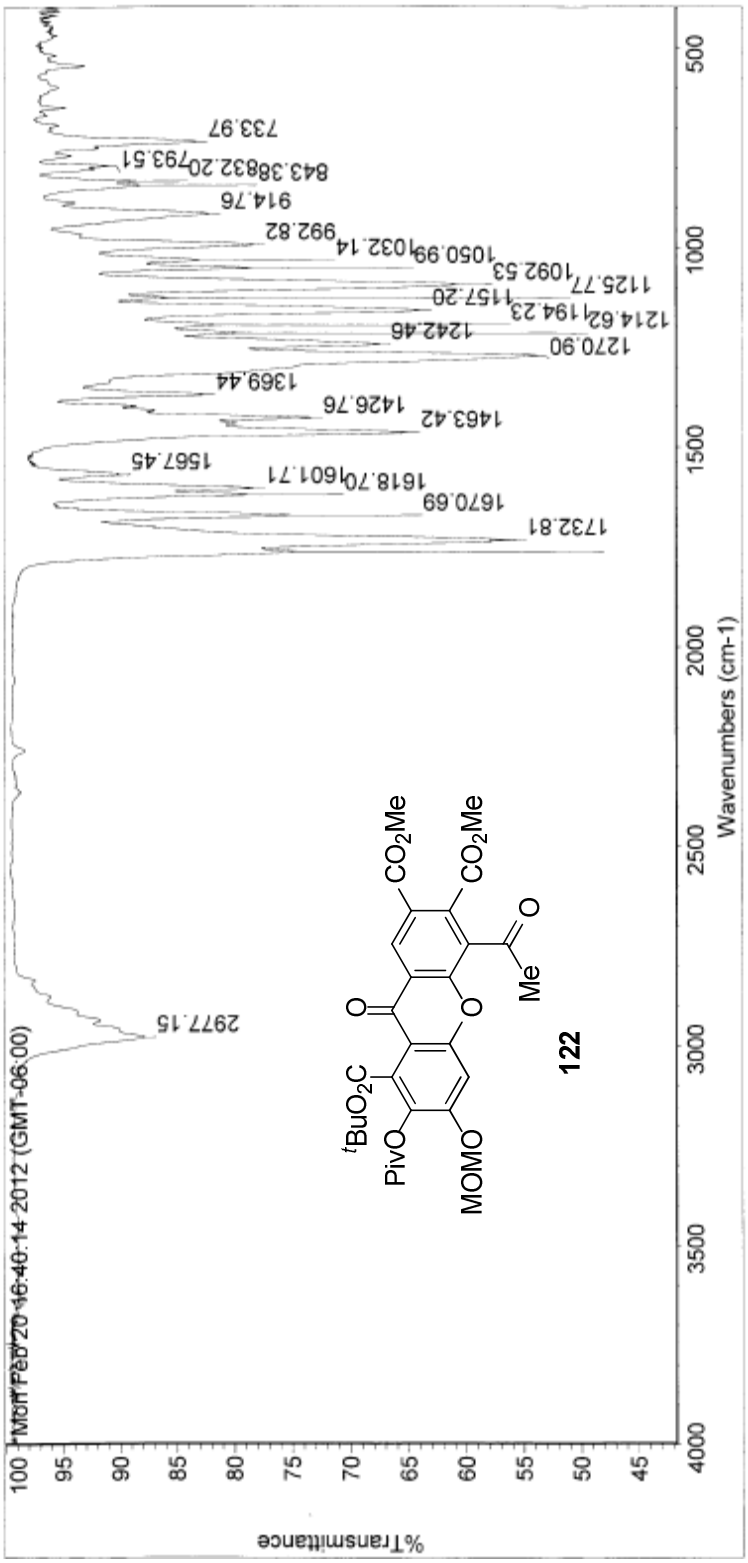


122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1214.62
1194.23
1157.20
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832.20
793.51
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CO2Me
O
Me
O
O
tBuO2C
PivO
MOMO

122

References.

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Chapter 3

Total Synthesis of Xanthofulvin and Structural Reassignment of 411J

In the paper suggesting the dimerization of two C_{14} polyketides in the biosynthetic pathway for the formation of vinaxanthone (**1**), a new natural product called 411J (**123**) was disclosed.[1] Interestingly, the spectral data for 411J (**123**) in both keto and enol forms matched that of xanthofulvin (**2**). In addition to our goal of synthesizing xanthofulvin (**2**), ambiguity in the structural assignment of 411J (**123**) could be cleared through the synthesis of xanthofulvin (**2**), the most plausible of the two structures (Figure 1).

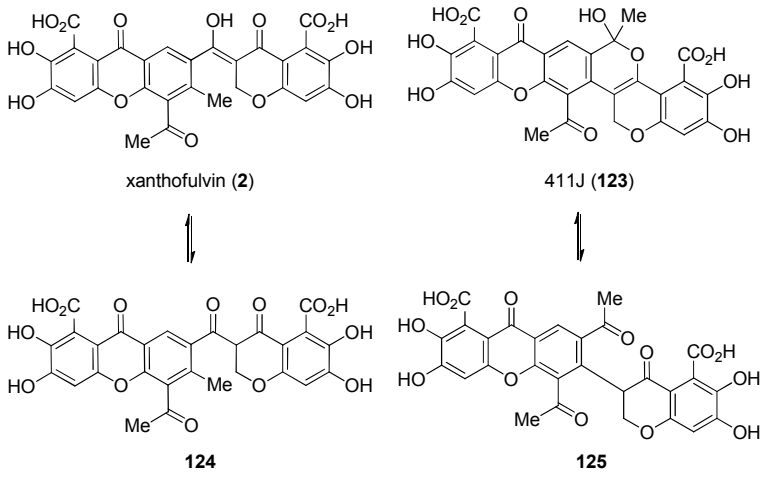


Figure 20. Equilibrating structures of xanthofulvin (**2**) and 411J (**123**) and their keto forms.

Applying the proposal for the formation of vinaxanthone (**1**) and dehydroxanthofulvin **63**, a postulated biosynthetic pathway can be seen for the *direct* synthesis of xanthofulvin (**2**) and one that accounts for the hemiketal in the proposed structure of 411J (**123**). In this pathway, Michael addition of polivione (**33**) into 5,6-dehydropolivione (**53**) forms adduct (**126**) undergoing elimination to form isomeric alkenes **126** and **127** (Figure 2).[2-5]

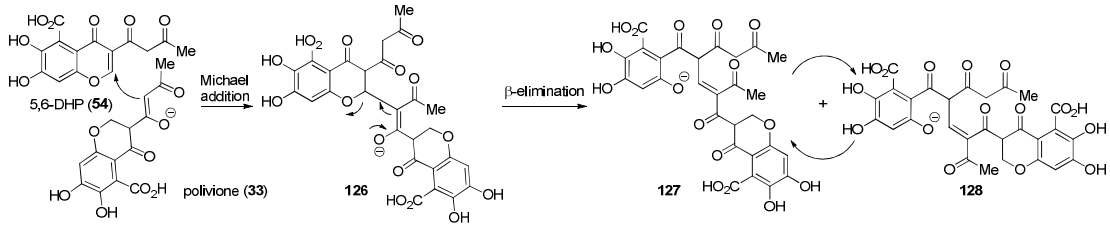


Figure 21. Initial adduct formation between 5,6-DHP (**53**) and polivione (**33**).

These isomers can interconvert readily at biological pH through anion **129** (Figure 3).

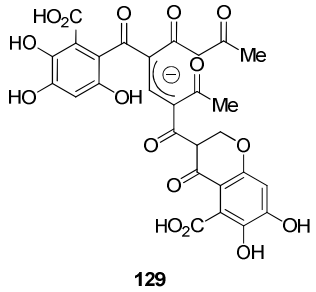


Figure 22. Highly delocalized tetraketo anion **129**.

Alkenes **127** and **128** can then undergo condensation to chromones **130** and **131**, which can interconvert due to extended conjugation. Structures **130** and **131**, are poised to react and cyclize (Figure 4).

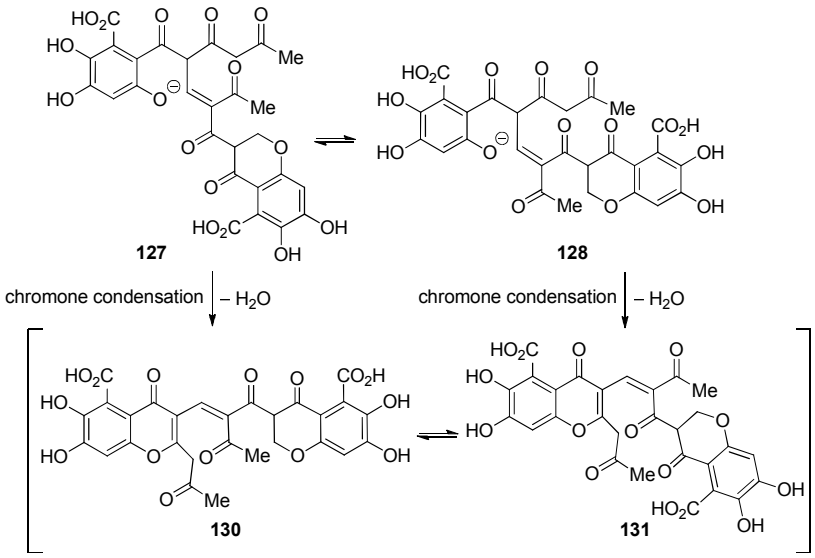


Figure 23. Chromone condensation of **127** and **128**.

It is likely they react in a 6π- electrocyclization and in the event **130** and **131** tautomerize to their trienol forms undergoing electrocyclization to form **134** and **135** (Figure 5).

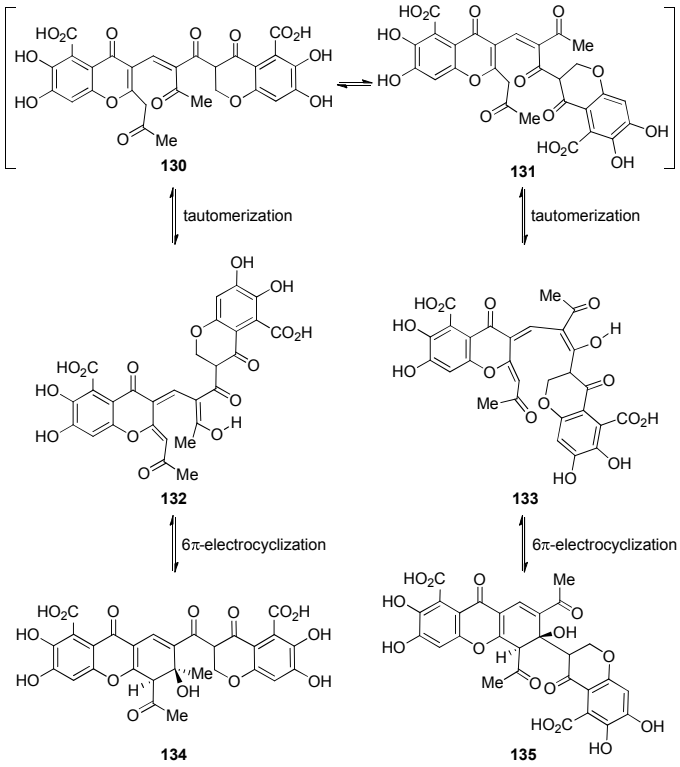


Figure 24. Tautomerization and 6π-electrocyclization reactions to form **134** and **135**.

The resultant aldol-like adducts **134** and **135** undergo dehydrative elimination to furnish the aromatized adducts providing vinaxanthone (**2**) or 411J (**123**) (Figure 6).

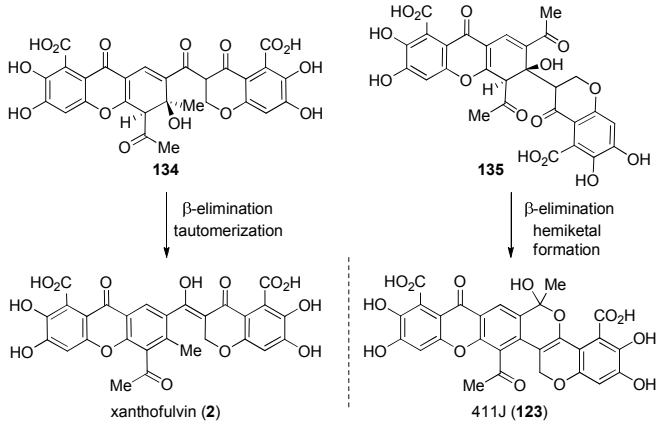


Figure 25. Formation of xanthofulvin (**2**) and 411J (**123**).

Initial experiments with this proposed biosynthetic pathway in the laboratory failed to furnish xanthofulvin (**2**) or 411J (**123**). It is known that polivione (**33**) is unstable and was never re-isolated from any of the reaction mixtures.[6] Based upon these results, the biomimetic cascade approach to xanthofulvin (**2**) was modified. A central focus was to incorporate a biomimetic 6π-electrocyclization in the synthesis of the tricyclic flank.[7] Retrosynthetically, xanthofulvin (**2**) was simplified to enedione **101** through sequential protecting group and reduction transforms (Figure 7).

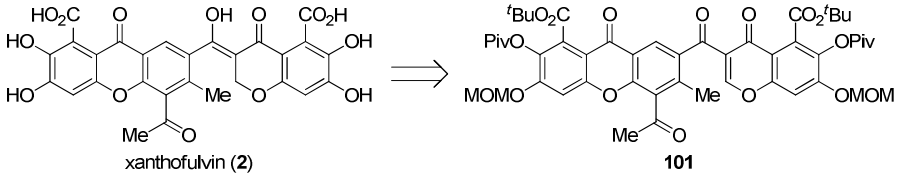


Figure 26. Retrosynthesis of xanthofulvin (**2**).

Enedione **101** can be simplified to enaminone **93** and carboxylic acid **136** through reduction and *O*→*C* carboxyl transfer transforms. Carboxylic acid **136** can be formed the methyl ester **137** (Figure 8).

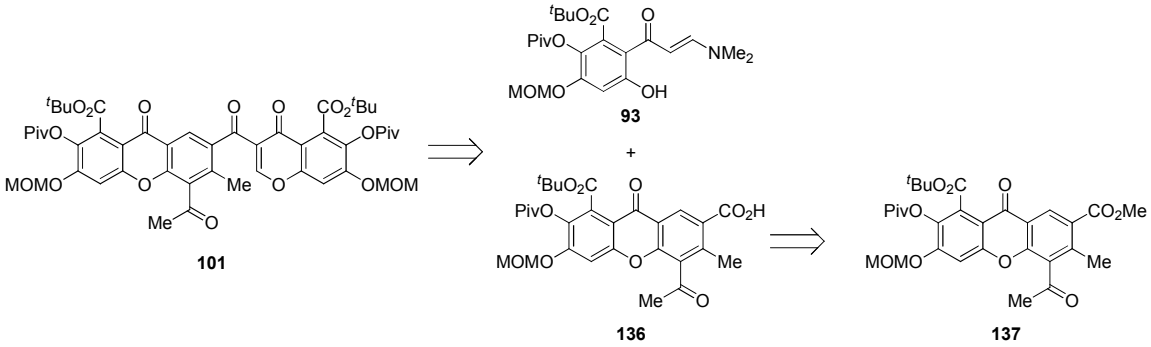


Figure 27. Retrosynthesis to subtargets **93** and **137**.

At this point the major objective was to develop a synthesis of methyl ester **137** and initial efforts were focused on advancing ketal **138** through a 6π-electrocyclization to arrive at **140** (Figure 9).[8]

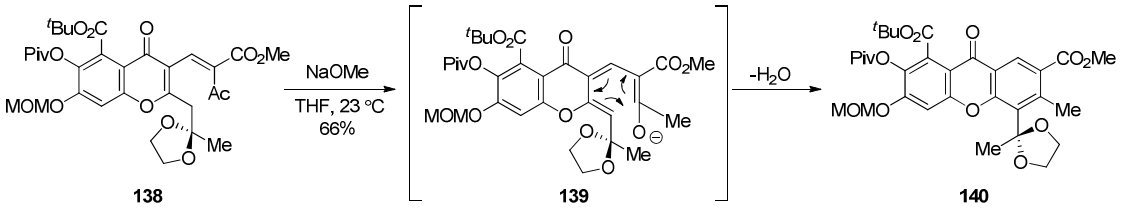


Figure 9. Electrocyclization route to tricyclic methyl ester **140**.

While this approach was satisfactory, it suffered from significant drawbacks. Deprotection of the ketal was accompanied by loss of the methoxymethyl protecting group complicating purification and would require *reinstallation* of a protecting group, something considered to be avoidable at this stage in the synthesis. Saponification of the methyl ester was extremely sluggish and hydrolysis of the pivaloyl ester was competitive. Additionally, this transformation was not scalable. Fortuitously, an interesting transformation involving 3-alkynyl chromanones was found to be a possible solution to this tricyclic methyl ester problem. This reaction, published by Hu and coworkers, is the addition of a stabilized nucleophile (β-ketoesters or β-diketones) into the 2-position of a 3-alkynyl chromanone.[9-11] This is an extension of known reactivity of 3-formyl or 3-ketonic chromanones.[12,13] The parent transformation, and the substrate which suggested this to be a feasible option is shown (Figure 10).

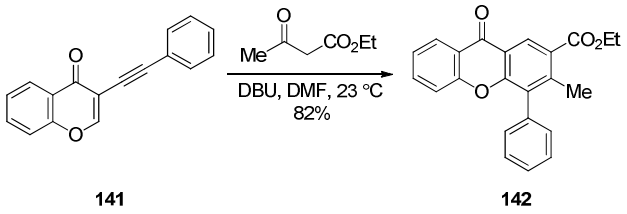


Figure 10. Formation of substituted tetracycle **142** from 3-alkynyl chromanone by Hu and co-workers.[9-11]

Interestingly, the only substrates reported in this paper contained terminal aryl or alkyl groups but the use of ynone **104** as a Michael acceptor was extended to this transformation. The reaction was run with methyl acetoacetate and the expected product **137** was obtained in a low, but significantly important yield (Figure 11).

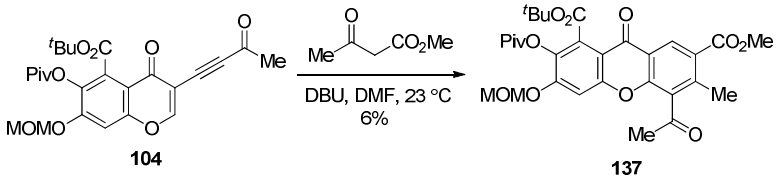
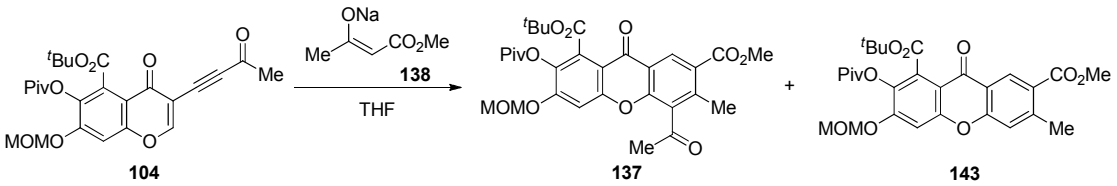


Figure 11. Initial rearrangement with ynone **95**.

The focus now was to optimize this transformation into something synthetically useful. A brief screen of bases found sodium hydride to be competent and better results were found by forming the sodium enolate **138** of methyl acetoacetate prior to addition into a solution of ynone **104**. THF was found to be the optimal solvent. Optimization is summarized and the yields are of isolated, purified material (Figure 12).



Temp. °C	Equiv. Nu -	Ratio **137**/**143**
23 °C	2 equiv.	19/81
0 °C	1 equiv.	29/71
0 °C	2 equiv.	56/44
–78 °C	2 equiv.	83/17

Figure 12. Optimization of rearrangement reaction in the synthesis of tricyclic methyl ester **137**.

This transformation was found to be moderately scalable (500 mg) and furnished good quantities of methyl ester **137**. A proposed mechanism for the transformation is shown (Figure 13).

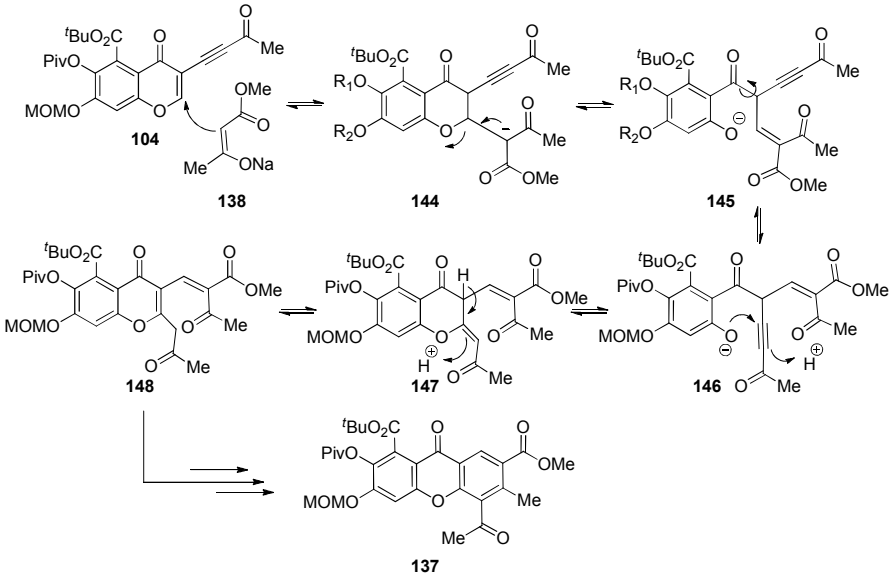


Figure 13. Proposed mechanism for the formation of tricyclic methyl ester **137**.

Saponification was accomplished with a slight excess (1.2 equiv.) of aqueous sodium hydroxide in THF furnishing carboxylic acid **136** as a white solid which did not require purification for subsequent steps (Figure 14).

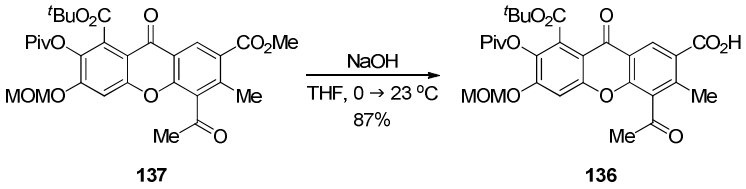


Figure 14. Hydrolysis of **137** to furnish carboxylic acid **136**.

This transformation, while straightforward, required extended reaction times of 30-40 hours. Increasting the equivalents of sodium hydroxide induced hydrolysis of *both* of the methyl and pivaloyl esters. The carboxylic acid **136** was reacted with oxalyl chloride in the presence of pyridine in benzene to afford the acid chloride **149**, which was taken on in crude form to the *O*→*C* carboxyl transfer step. These reaction conditions were chosen for mildness and the pyridinium chloride formed is insoluble in benzene and can be

filtered away. The carboxyl transfer was accomplished in moderate yield and several amine bases and solvents were used to determine the optimal conditions. All conditions employing acid chloride **149** were essentially equivalent with regard to yield. A representative result is shown (Figure 15).

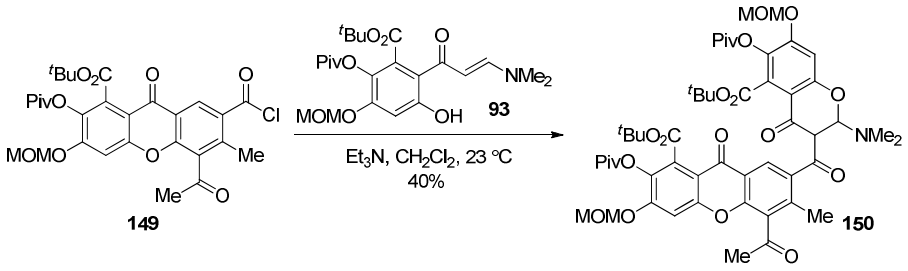


Figure 15. Carboxyl transfer reaction using acid chloride **149**.

The use of acid chlorides or other activated carboxylic acid surrogates, such as acyl imidazolides, have typically been employed for such transformations.[14-16] It was thought that the use of the free carboxylic acid with a coupling reagent might furnish the product in greater yield. Additionally, this would eliminate the step of preparing the acid chloride. The use of DCC or EDCI showed an improvement in yield compared to the acid chloride strategy, furnishing aminal **150** in 60% yield. However, chromatographic purification became tedious to remove the urea byproducts and work up conditions were not amenable to urea separation due to the basicity of the aminal. The use of PyBOP or similar reagents showed no improvement beyond the yields found with the acid chloride strategy. Employing HBTU showed a *significant* improvement in the yield of this transformation, furnishing aminal **150** in high yield through the presumed intermediate phenolic ester **151**.[17] To the best of our knowledge this is the first example of an enaminone $O \rightarrow C$ carboxyl transfer reaction proceeding directly with a carboxylic acid,

and this is one of the most hindered substrates applied to this type of transformation (Figure 16).

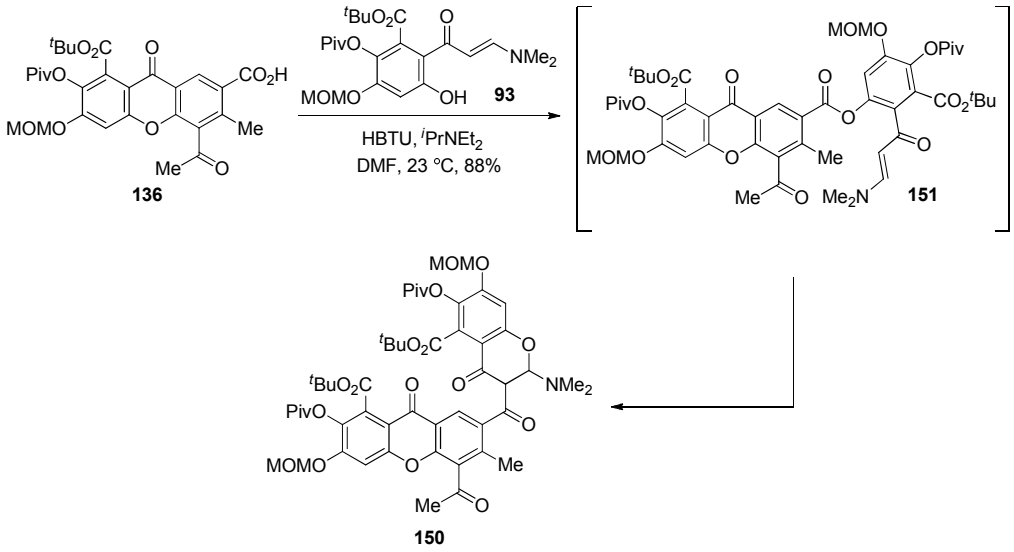


Figure 16. Carboxyl transfer using carboxylic acid **136** to form aminal **150**.

Additionally, this reaction does not require chromatographic purification. Workup with an admixture of hexanes and ethyl acetate and saturated LiCl washings furnish material of high purity which can be taken on to subsequent steps with no decrease in yield. This has allowed for the late stage advancement of 2-3 gram batches of aminal **150**. Transforming aminal **150** into enedione **101** now became the next task. Spectroscopically, aminal **150** displays a 13.3 Hz coupling constant for the chromanyl methine proton flanked by the two carbonyl groups (Figure 17).

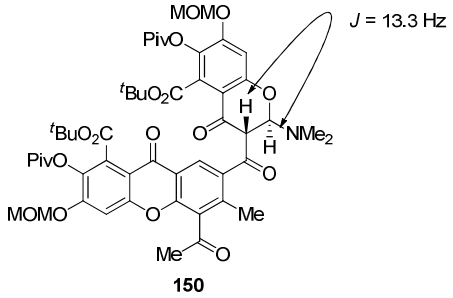


Figure 17. Aminal **150** stereochemistry.

This is highly suggestive of a *trans* diaxial relationship and it was thought that thermolysis of **150** would induce a *syn*-elimination of dimethylamine to furnish enedione **101**. Heating a solution of aminal **150** in toluene at reflux did not induce elimination and only starting material was recovered even after extended reaction times (Figure 18).

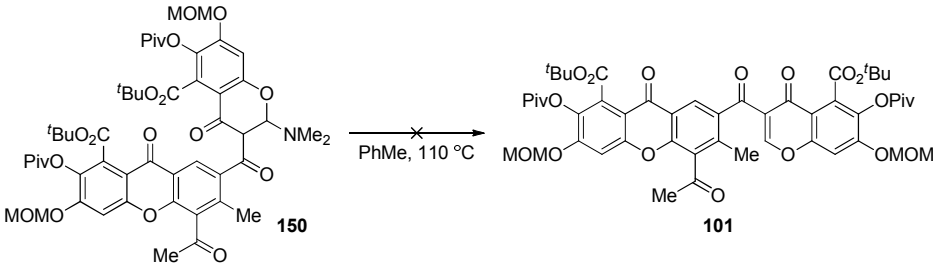


Figure 18. Attempt at thermal elimination to form enedione **101**.

Attention was now focused on an acid promoted elimination to furnish enedione **101**. A brief screen of Brønsted acids showed pyridinium chloride to be the most effective, and that acetonitrile was the optimal solvent. Other Brønsted acids were either ineffective, returning unreacted starting material, or were too vigorous promoting cleavage of the protecting groups (Figure 19).

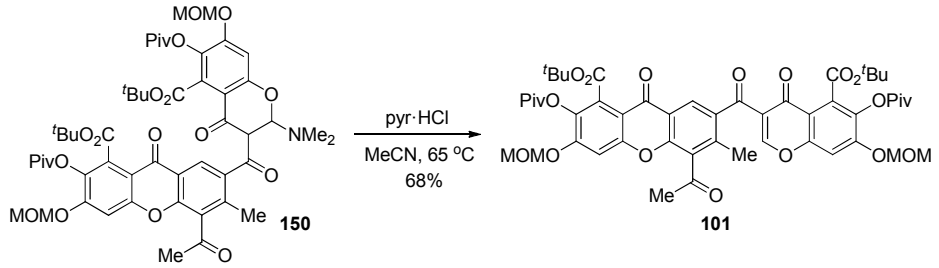
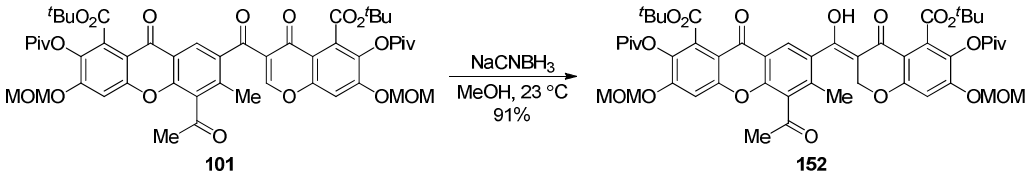


Figure 19. Formation of enedione **135**.

Examining conditions for the reduction of chromanyl enediones found that borohydrides are generally useful.[18,19] Reduction of enedione **101** was accomplished under the action of $NaCNBH_3$ in MeOH to smoothly, and rapidly (20 min.), furnishing

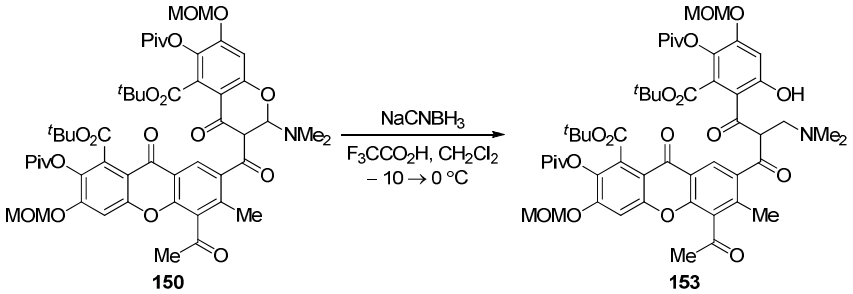
protected xanthofulvin **152**. This reaction has also been scaled to over 300 mg (Figure 20).



101 **152**

Figure 20. Reduction of **101** to form protected xanthofulvin **152**.

It should be noted that attempts were made to convert aminal **150** directly to protected xanthofulvin **152** through reduction of the dimethylamino moiety. The use of silane reductants failed to furnish the desired product **152** and returned unreacted starting material, and the use of borohydride reductants furnished the reductive amination product **153** in high yield (Figure 21).



150 **153**

Figure 21. Attempted reduction of aminal **152** to form protected xanthofulvin **155**.

There is ample literature precedent for reduction where the aminal nitrogen is endocyclic and the oxygen substituent is exocyclic.[20] However, to the best of our knowledge there is no literature precedent for the opposite case where the aminal nitrogen is exocyclic (Figure 22).

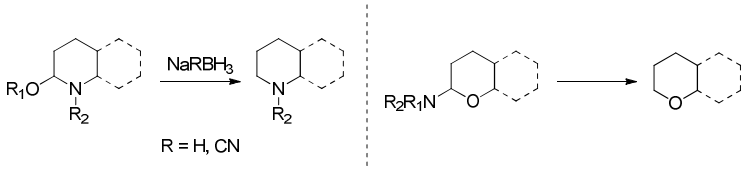


Figure 22. Endocyclic and exocyclic aminals.

In the absence of acid, reduction occurred with borohydride reagents. It is likely that the aminal ionized to the zwitterionic, releasing the phenoxide and the dimethylamino iminium was reduced rapidly in the presence of hydride.

The final step, deprotection of all oxygen bound protecting groups was accomplished with BCl_3 in methylene chloride in high yield to furnish synthetic xanthofulvin (**2**) as a bright yellow solid. It is of note that this is an interesting example of an aryl pivaloate deprotection accomplished under non-basic conditions.[21] (Figure 23).

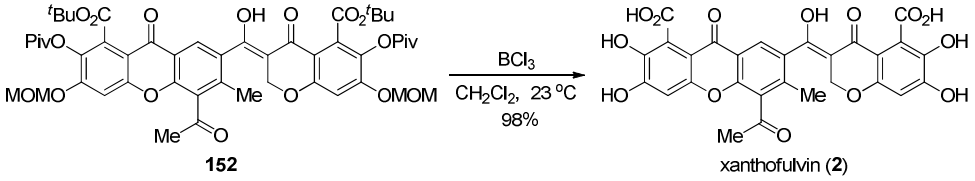


Figure 23. Formation of xanthofulvin (**2**).

Synthetic xanthofulvin matched all reported spectral values for isolated xanthofulvin (**2**) and 411J (**123**).[22] The first total synthesis of xanthofulvin (**2**) and the accompanied structural reassignment of 411J (**123**) to that of xanthofulvin (**2**) has been accomplished.[23]

Current efforts are focused on the synthesis of analogs. The strategy of using an advanced tricycle and vinylogous amide allows for the synthesis of 64 possible xanthofulvin analogs based on the arene substitution patterns (Figure 24).

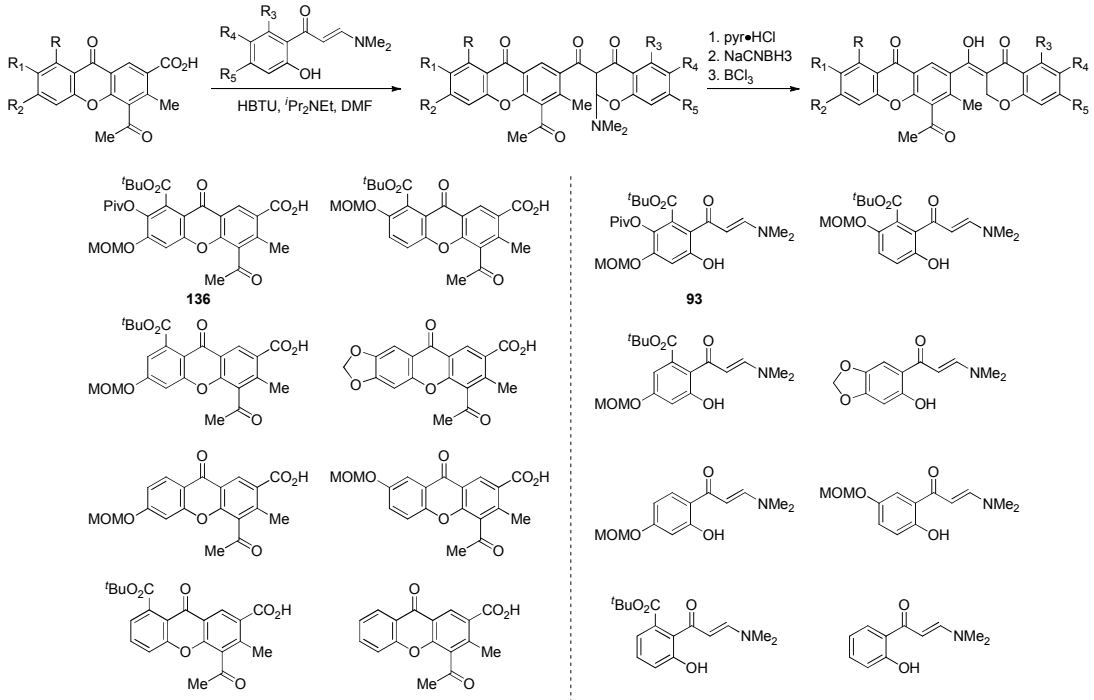
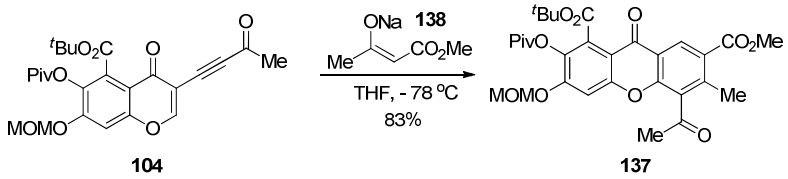


Figure 24. Monomers to be used in the synthesis of chemically edited xanthofulvin (**2**) analogs.

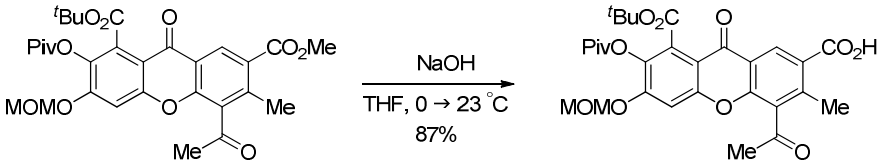
Selective deletion of a phenolic residue or carboxylic acid will furnish a library of chemically edited derivatives. These analogs will help elucidate the exact mechanism of action of xanthofulvin (**2**) through structure-activity relationship studies and target identification.

Experimental Section



To a stirred suspension of sodium hydride (60% dispersion in mineral oil, 556 mg, 13.9 mmol, 1.0 equiv.) in THF (55.7 mL) was added methyl acetoacetate (1.50 mL, 13.9 mmol, 1.0 equiv.) dropwise over 5 minutes to furnish a 0.25 M stock solution of the sodium enolate of methyl acetoacetate (stored in a schlenk flask under argon). To a stirred solution of ynone **104** (500 mg, 1.06 mmol, 1.0 equiv.) in THF (88 mL) at −78 °C was added a solution of the sodium enolate of methyl acetoacetate (0.25 M THF, 8.50 mL, 2.12 mmol, 2.0 equiv.) **138** dropwise down the side of the flask over 10 minutes. Upon complete addition the red-amber solution was allowed to stir at −78 °C and after 5 h, the excess sodium enolate of methyl acetoacetate was quenched with aqueous HCl (1.0 M, 1.5 mL). The resulting yellow solution was diluted with EtOAc (150 mL), washed with water (3 x 50 mL), brine (50 mL), dried over sodium sulfate, and concentrated *in vacuo*. The yellow residue was chromatographed on silica gel (3:1 hexanes/EtOAc) to furnish methyl ester **137** (502 mg, 83 %) as a tan solid (m.p. 199-201 °C).

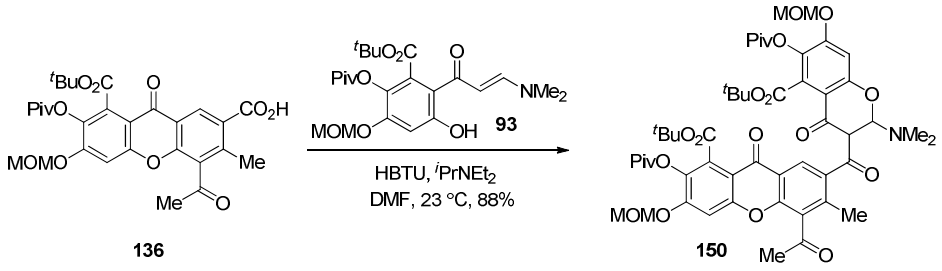
R_f = 0.40 (silica gel, hexanes/EtOAc = 2:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.84 (s, 1H), 7.17 (s, 1H), 5.27 (s, 2H), 3.93 (s, 3H), 3.47 (s, 3H), 2.67 (s, 3H), 2.62 (s, 3H), 1.67 (s, 9H), 1.39 (s, 9H); **^{13}C NMR** (100 MHz, CD_2Cl_2): δ 202.4, 175.9, 173.6, 166.6, 163.8, 154.8, 154.7, 153.4, 142.8, 135.8, 133.2, 129.9, 129.0, 127.6, 119.3, 112.7, 103.9, 95.1, 83.5, 56.9, 52.6, 39.5, 32.9, 28.3, 27.4, 18.2; **IR** (film, υ cm^{-1}): 1760, 1735, 1663, 1599; **HRMS** (ESI) calcd. for $C_{30}H_{34}O_{11}Na^+$ $[M+Na]^+$: 593.19933. Found: 593.19976.



127 **136**

To a stirred solution of methyl ester **127** (920 mg, 1.61 mmol, 1.0 equiv.) in THF (65 mL) at 0 °C was added aqueous sodium hydroxide (0.1 M, 19.4 mL, 1.94 mmol, 1.20 equiv.) dropwise over 2 minutes. Upon complete addition the gold-orange solution was allowed to warm to 23 °C. After 36 h the reaction was diluted with water (100 mL). The solution was washed with ether (3 x 50 mL) and the aqueous layer was acidified by addition of 0.1 M HCl aq. (20 mL). The clear aqueous layer was extracted with EtOAc (3 x 250 mL), dried over sodium sulfate and concentrated *in vacuo* to furnish carboxylic acid **136** (780 mg, 87%) as a white solid (mp: 203-204 °C) that was used in the next step without purification.

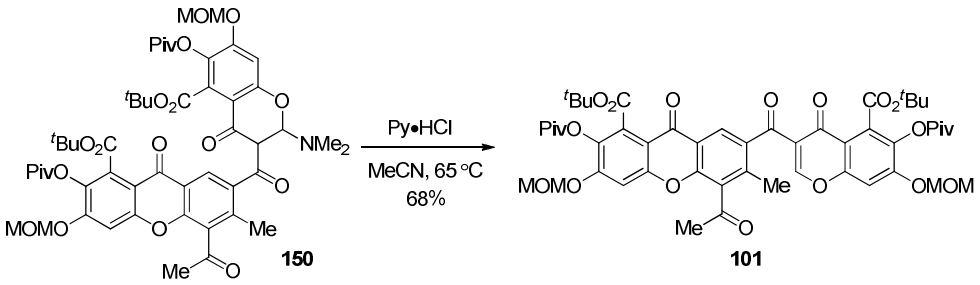
^{1}H NMR (400 MHz, $CDCl_3$): δ 8.98 (s, 1H), 7.17 (s, 1H), 5.27 (s, 2H), 3.47 (s, 3H), 2.69 (s, 3H), 2.65 (s, 3H), 1.67 (s, 9H), 1.39 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 202.3, 175.6, 173.2, 168.9, 163.5, 154.5, 154.4, 153.6, 143.1, 135.8, 133.0, 131.4, 129.0, 125.7, 119.2, 112.8, 103.7, 94.8, 83.4, 56.7, 39.2, 32.8, 28.2, 27.3, 18.3; **IR** (film, υ cm^{-1}): 1760, 1688, 1666, 1619, 1596; **HRMS** (ESI) calcd. for $C_{29}H_{32}O_{11}Na^+$ $[M+Na]^+$: 579.18368. Found: 579.18373.



To a stirred solution of carboxylic acid **136** (373 mg, 0.67 mmol, 1.10 equiv.) in DMF (3.0 mL) at 23 °C was added solid *O*-(benzotriazol-1-yl)-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate (254 mg, 0.67 mmol, 1.1 equiv.) in one portion followed by N,N-diisopropylethylamine (0.27 mL, 1.52 mmol, 2.5 equiv.). The dark amber solution was stirred for 5 min. and then solid enaminone **93** (275 mg, 0.61 mmol, 1.10 equiv.) was added in one portion. The reaction was stirred for 6 h then diluted with 1:1 hexanes/EtOAc (100 mL) and washed with saturated aqueous LiCl solution (8 x 30 mL). The organic layer was dried over sodium sulfate and concentrated *in vacuo*. The tan residue was chromatographed on silica gel (1:2 hexanes/EtOAc with 2% Et_3N) to furnish aminal **150** (528 mg, 88 %) as a dark yellow solid (m.p. 124-126 °C).

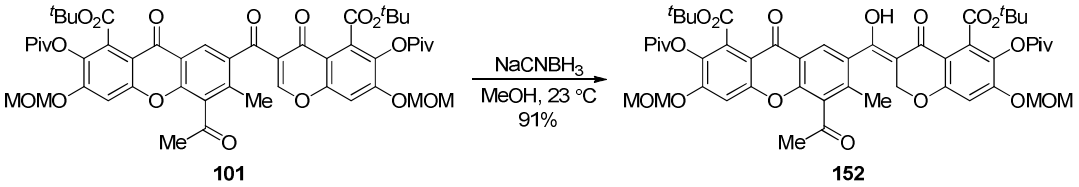
R_f = 0.25 (silica gel, hexanes/EtOAc = 1:1, 2% Et_3N); **^{1}H NMR** (400 MHz, $(CD_3)_2CO$): δ 8.87 (s, 1H), 7.42 (s, 1H), 7.30 (s, 1H), 5.46 (s, 2H), 5.28 (s, 2H), 5.23 (d, *J* = 13.3 Hz, 1H), 3.47 (s, 3H), 3.44 (s, 3H), 3.07 (s, 3H), 2.86 (d, *J* = 13.3 Hz , 1H), 2.74 (s, 3H), 2.72 (s, 3H), 2.59 (s, 3H), 1.64 (s, 9H), 1.44 (s, 9H), 1.37 (s, 9H), 1.35 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 202.2, 175.5, 175.3, 173.0, 163.9, 163.5, 157.5, 154.8, 154.5, 154.4, 153.4, 149.4, 144.9, 143.2, 136.4, 136.3, 135.7, 132.9, 130.9, 128.9, 128.8, 126.1, 120.1, 119.1, 112.7, 111.6, 103.6, 94.8, 94.7, 83.2, 83.1, 82.5, 56.7, 56.3, 44.9, 39.2, 39.0, 36.9,

32.8, 28.1, 27.7, 27.2, 27.1, 18.1; **IR** (film, υ cm^{-1}): 1766, 1730, 1660, 1610; **HRMS** (ESI) calcd. for $C_{52}H_{63}NO_{18}Na^+$ $[M+Na]^+$: 1012.39374. Found: 1012.39398.



To a stirred solution of aminal **150** (83.6 mg, 0.084 mmol, 1.0 equiv.) in acetonitrile (5.6 mL) was added solid pyridinium chloride (49 mg, 0.42 mmol, 5.0 equiv.) in one portion and the resulting yellow solution was heated to 65 °C. After 18 h the reaction was concentrated and the yellow residue was chromatographed on silica gel (3:1 hexanes/EtOAc →2:1 hexanes/EtOAc to furnish enedione **101** (54 mg, 68%) as a clear-yellow solid (m.p. 185-188 °C).

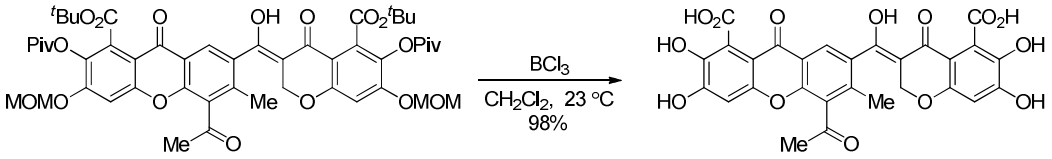
R_f = 0.21 (silica gel, hexanes/EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.43 (s, 1H), 8.25 (s, 1H), 7.27 (s, 1H), 7.17 (s, 1H), 5.26 (s, 4H), 3.48 (s, 3H), 3.47 (s, 3H), 2.68 (s, 3H), 2.45 (s, 3H), 1.61 (s, 9H), 1.42 (s, 9H), 1.38 (s, 9H), 1.35 (s, 9H); **^{13}C NMR** (125 MHz, $CDCl_3$): δ 202.2, 192.1, 175.5, 175.3, 173.2, 172.1, 163.5, 162.9, 160.4, 154.6, 154.4, 154.3, 153.7, 152.6, 140.6, 136.8, 136.4, 135.6, 132.3, 128.9, 128.6, 127.3, 123.8, 118.7, 116.5, 112.7, 104.0, 103.6, 94.8, 94.7, 83.2, 83.1, 56.7, 56.6, 39.2, 39.1, 32.7, 28.2, 27.9, 27.3, 27.2, 17.5; **IR** (film, υ cm^{-1}): 1760, 1732, 1663, 1607, 1591; **HRMS** (ESI) calcd. for $C_{50}H_{56}O_{18}Na^+$ $[M+Na]^+$: 967.33589. Found: 967.33504.



101 **152**

To a stirred solution of endione **101** (30 mg, 0.032 mmol, 1.0 equiv.) in methanol (0.64 mL) at 23 °C was added solid sodium cyanoborohydride (4.0 mg, 0.063 mmol, 2.0 eq) in one portion. After 20 minutes the chalky yellow reaction mixture was diluted with aqueous pH 7.0 phosphate buffer (0.2 M, 0.25 mL) then diluted with EtOAc (10 mL). The organic phase was separated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic layers were washed with brine (10 mL), dried over sodium sulfate, and concentrated *in vacuo*. The yellow reside was chromatographed on silica gel (2:1 hexanes/EtOAc) to afford protected xanthofulvin **152** (27 mg, 91 %) as a bright yellow solid (mp: 184-186 °C).

R_f = 0.5 (silica gel, hexanes/EtOAc = 1:1); **^{1}H NMR** (400 MHz, $CDCl_3$): δ 15.43 (s, 1H), 8.12 (s, 1H), 7.18 (s, 1H), 6.68 (s, 1H), 5.28 (s, 2H), 5.16 (s, 2H), 4.74 (bs, 2H), 3.48 (s, 3H), 3.42 (s, 3H), 2.71 (s, 3H), 2.41 (s, 3H), 1.66 (s, 9H), 1.62 (s, 9H), 1.39 (s, 9H), 1.37 (s, 9H); **^{13}C NMR** (150 MHz, $CDCl_3$): δ 201.9, 183.6, 175.7, 173.3, 173.1, 163.9, 163.6, 160.0, 154.9, 154.5, 152.3, 139.6, 135.7, 133.4, 132.4, 130.3, 129.3, 128.9, 126.9, 119.2, 112.7, 111.9, 103.9, 103.8, 103.5, 94.8, 94.4, 93.4. 83.3, 82.9, 66.7, 56.7, 56.5, 39.2, 39.1, 32.7, 29.7, 28.2, 28.1, 27.3, 27.2, 16.9; **IR** (film, υ cm^{-1}): 1765, 1730, 1666, 1602, 1458; **HRMS** (ESI) calcd. for $C_{50}H_{58}O_{18}Na^+$ $[M+Na]^+$: 969.35154. Found: 969.35120.

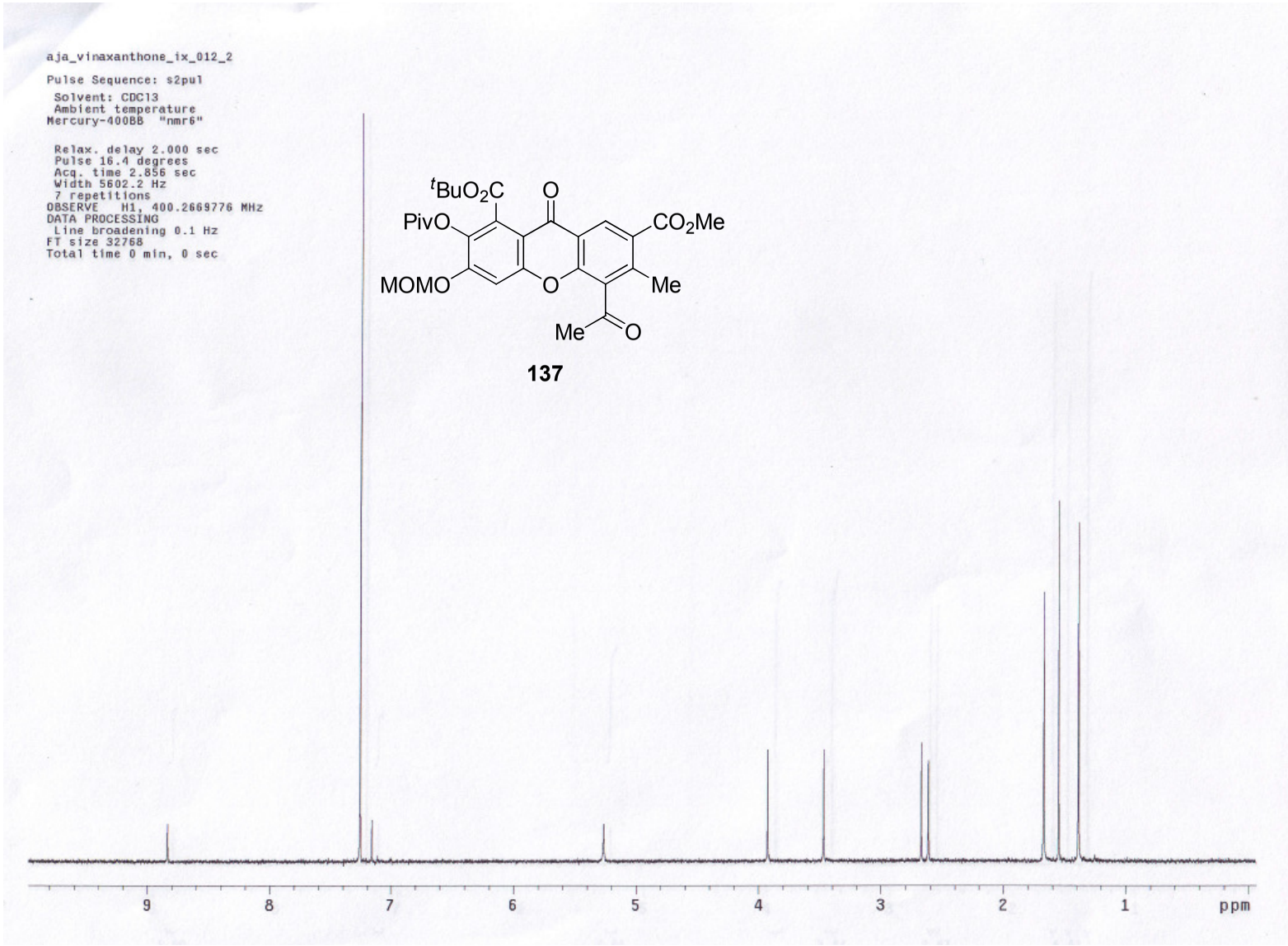


152 xanthofulvin (**2**)

To a stirred solution of protected xanthofulvin **152** (20 mg, 0.02 mmol, 1.0 equiv.) in dry methylene chloride (2.1 mL) at 23 °C was added a solution of boron trichloride (1.0 M CH_2Cl_2, 0.25 mL, 0.25 mmol, 12 eq) and the reaction was stirred for 45 minutes then the yellow-orange solution was treated with aqueous HCl (12 M, 0.09 mL) and diluted with ethyl acetate (10 mL). The bright orange solution was stirred vigorously for 15 minutes and then concentrated *in vacuo.* The orange residue was diluted with methanol (15 mL) and re-concentrated *in vacuo*. The yellow residue was triturated with cholorform (10 mL) and then filtered. The yellow solid was then dried *in vacuo* to furnish xanthofulvin **(2)** (11.8 mg, 98%) as a 3.6:1 ratio of enol:keto tautomers as a bright yellow solid (m.p. 252-253 °C).

R_f = 0.14 (silica gel, EtOAc/AcOH = 20:1); **^{1}H NMR** (500 MHz, $(CD_3)_2SO$): **Enol**: δ 15.61 (s, 1H), 12.75 (s, 1H), 11.62 (s, 1H), 11.23 (s, 1H), 9.33 (s, 1H), 8.69 (s, 1H), 7.95 (s, 1H), 6.93 (s, 1H), 6.39 (s, 1H), 4.66 (s, 2H), 2.70 (s, 3H), 2.31 (s, 3H). **Keto**: δ 11.15 (s, 1H), 8.88 (s, 1H), 8.51 (s, 1H), 6.92 (s, 1H), 6.42 (s, 1H), 5.01 (dd, *J* = 4.7 Hz, 8.1 Hz, 1H), 4.71 (dd, *J* = 4.2 Hz, 11.3 Hz, 1H), 4.60 (m, 1H), 2.67 (s, 3H), 2.29 (s, 3H). **^{13}C NMR** (125 MHz, $(CD_3)_2SO$): **Enol**: 202.6, 183.7, 172.7, 172.7, 167.5, 167.5, 156.3, 154.5, 153.9, 152.2, 150.2, 140.8, 137.6, 132.4, 129.4, 128.3, 125.9, 120.7, 120.7, 118.7, 110.1, 104.4, 102.4, 102.4, 65.9, 32.4, 16.6. **Keto**:

δ 202.9, 199.1, 186.3, 172.7, 167.7, 167.7, 156.3, 154.7, 153.9, 152.2, 150.1, 140.9, 139.2, 137.6, 134.9, 132.4, 127.7, 122.2, 120.8, 118.3, 110.1, 108.8, 102.4, 68.0, 56.3, 32.4, 17.1. ; **IR** (KBr, υ cm^{-1}): 3419, 2926, 1607, 1468, 1288, 1021; **HRMS** (ESI) calcd. for $C_{28}H_{17}O_{14}$ $[M-H]^-$: 577.06238. Found: 577.06186.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7 repetitions
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Me
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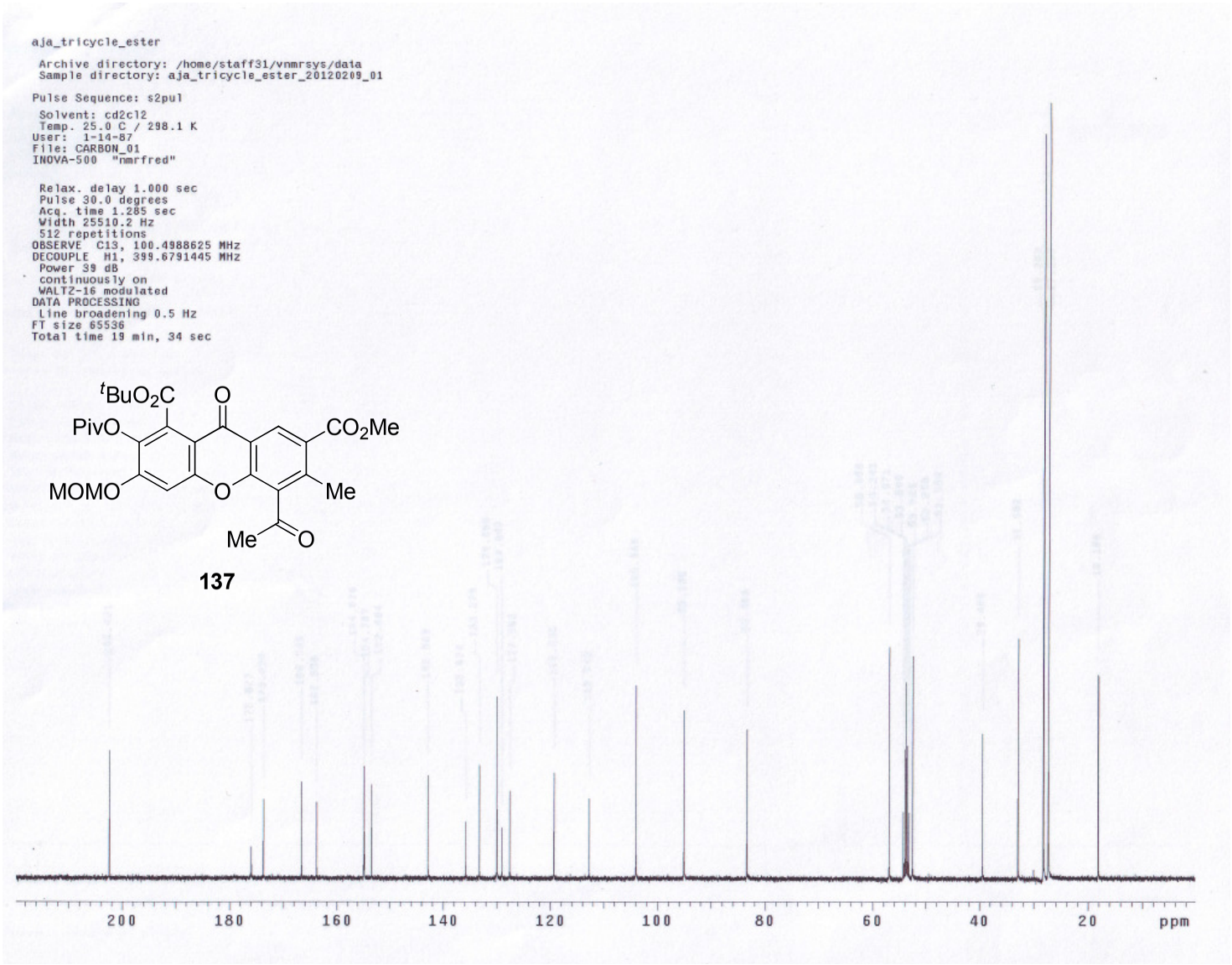
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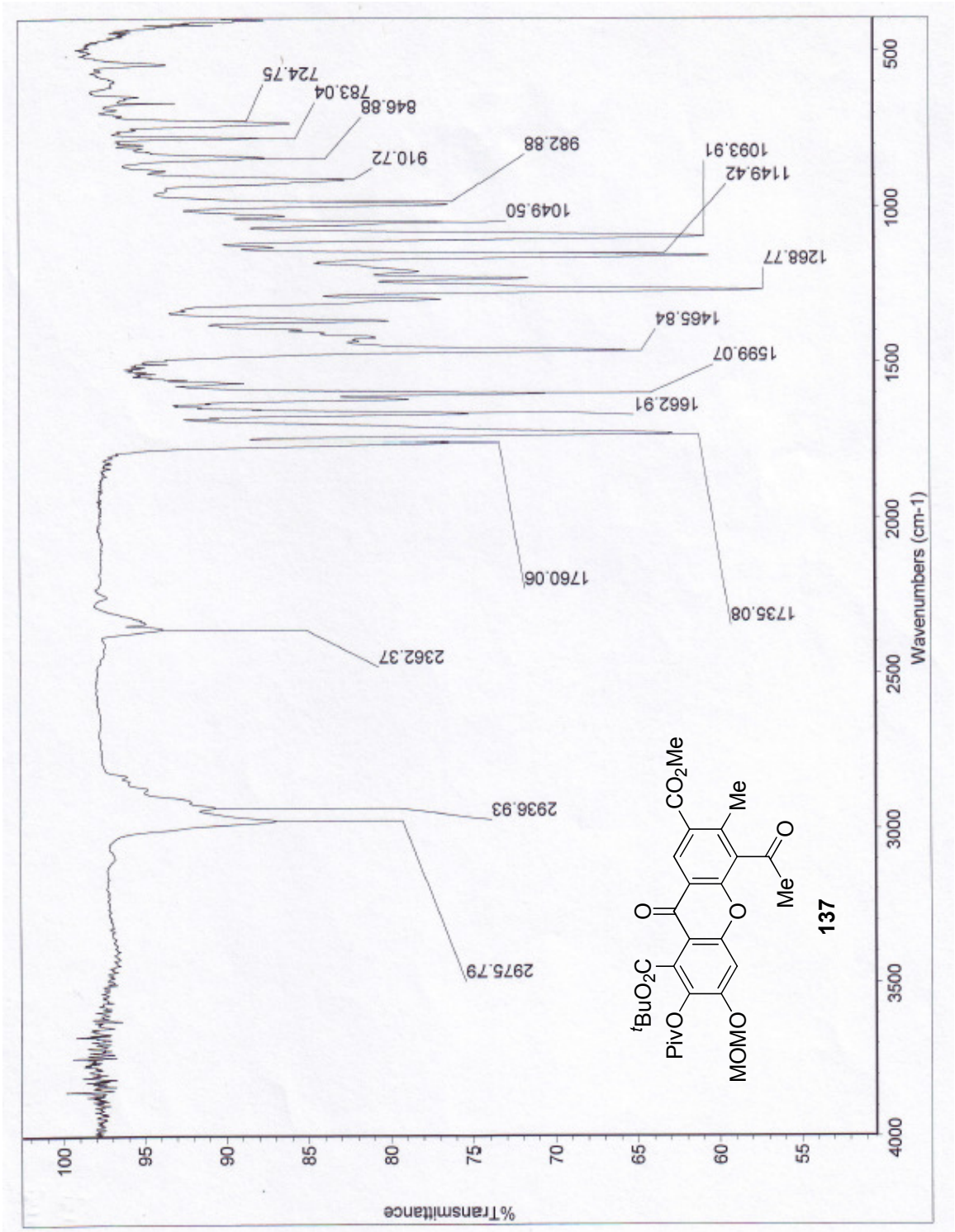
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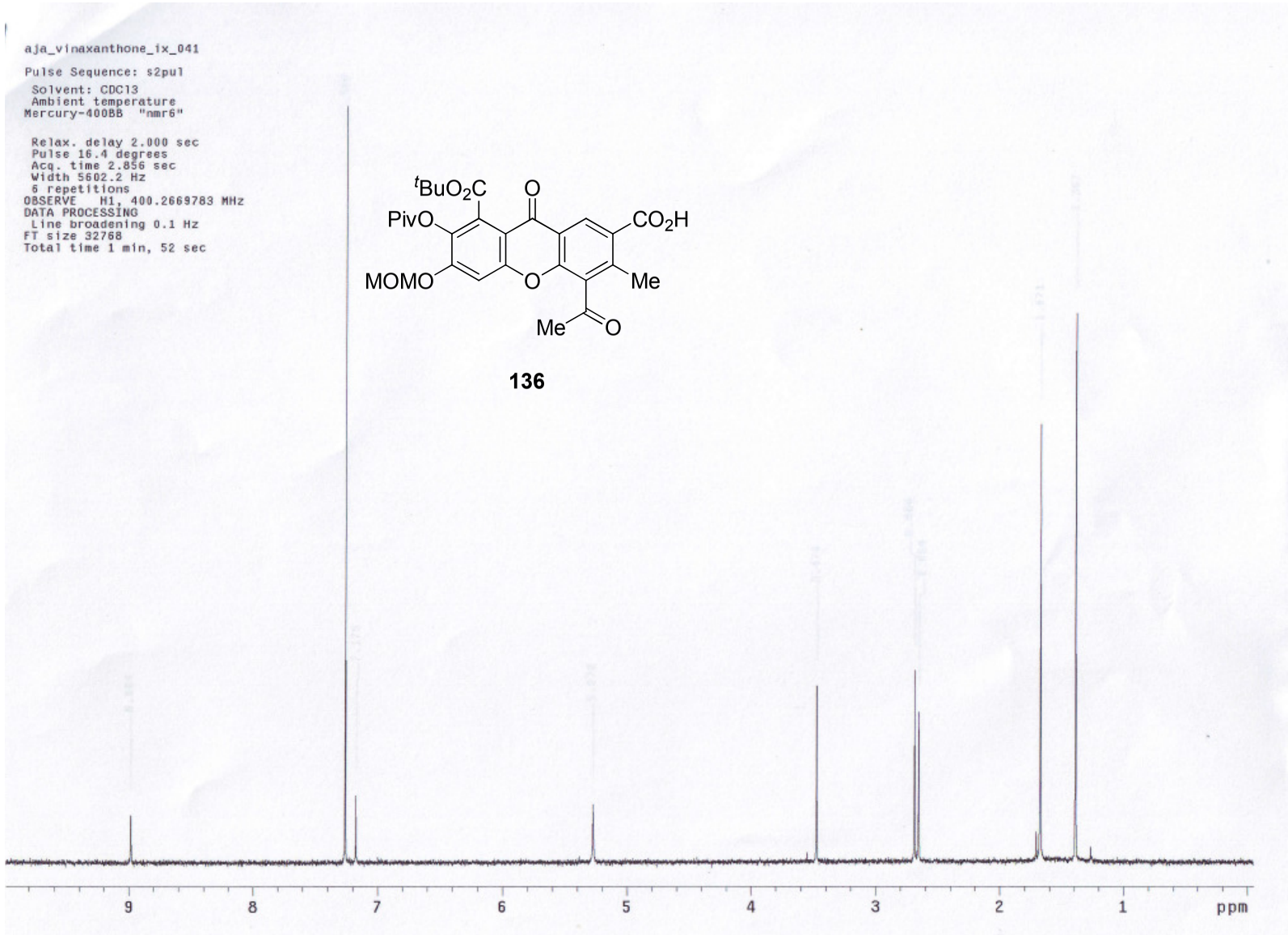
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OBSERVE H1, 400.2669783 MHz
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FT size 32768
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PivO
CO2H
MOMO
O
Me
Me
O
136
9
8
7
6
5
4
3
2
1
ppm

600 MHz nmrox

aja_tricycle_acid

exp4 Carbon

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bs	16	in	n
d1	2.000	dp	y
nt	13000	hs	nn
ct	13000	PROCESSING	
TRANSMITTER		lb	1.00
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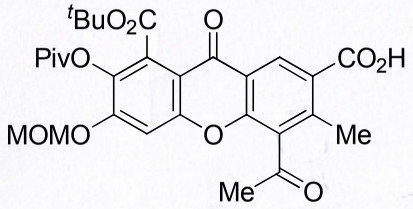
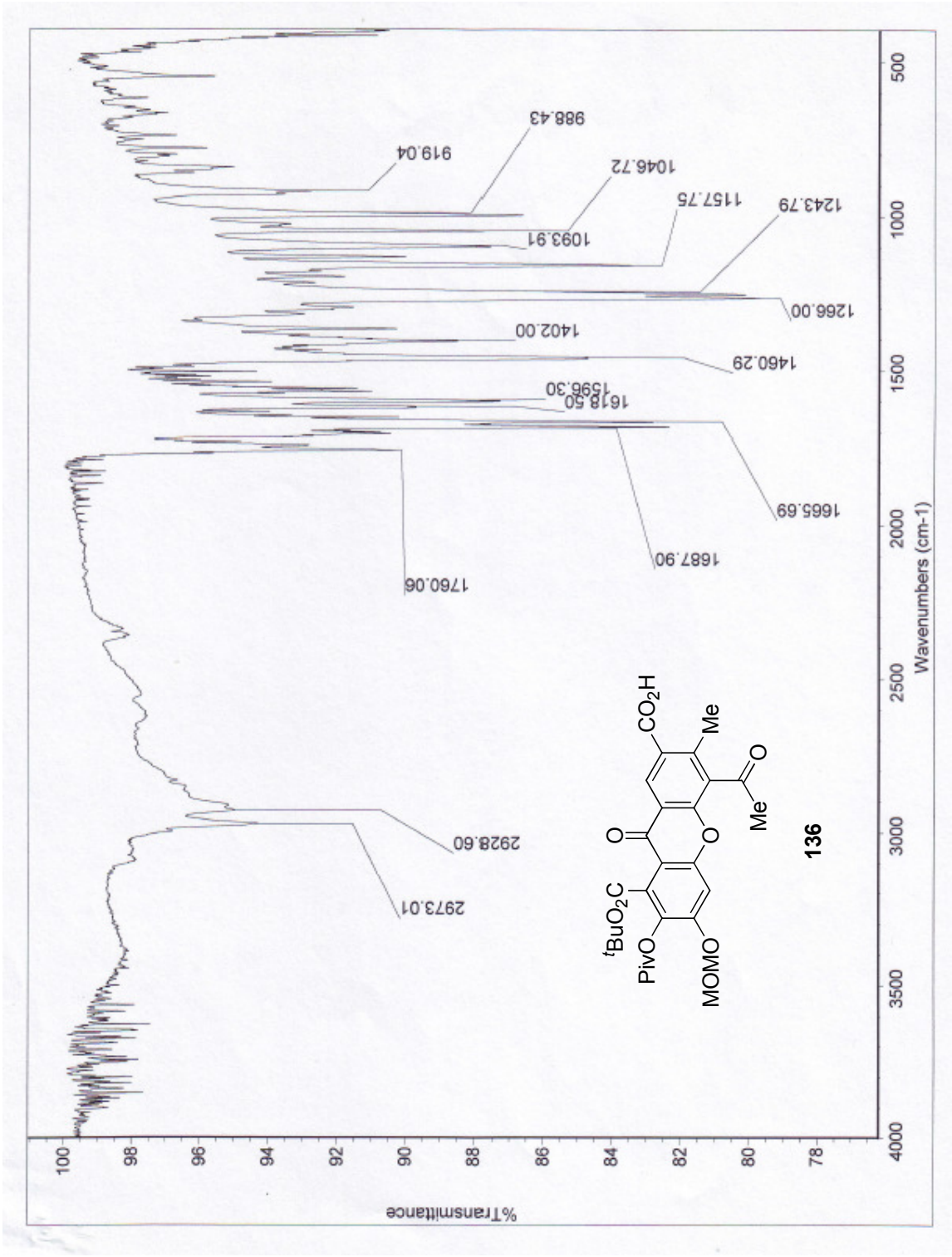
tof	2296.3	sp	-754.2
tpwr	58	wp	33931.4
pw	2.600	rfl	15180.6
DECOUPLER		rfp	11612.2
dn	H1	rp	-83.6
dof	0	lp	57.0
dm	yyy	PLOT	
dmm	w	wc	250
dpwr	46	sc	0
dmf	15337	vs	98633
		th	4
		ai cdc ph	



136


%Transmittance
Wavenumbers (cm-1)
4000
3500
3000
2500
2000
1500
1000
500
100
98
96
94
92
90
88
86
84
82
80
78
2973.01
2928.60
1760.06
1687.90
1665.69
1618.50
1596.30
1460.29
1402.00
1266.00
1243.79
1157.75
1093.91
1046.72
919.04
988.43
CO2H
Me
O
Me
O
O
tBuO2C
PivO
MOMO
136

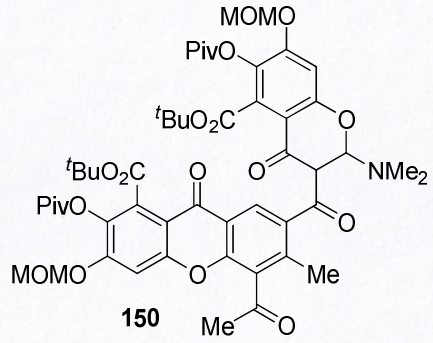
aja_aminal

Archive directory: /home/staff31/vnmrsys/data
Sample directory: aja_aminal_20120517_01

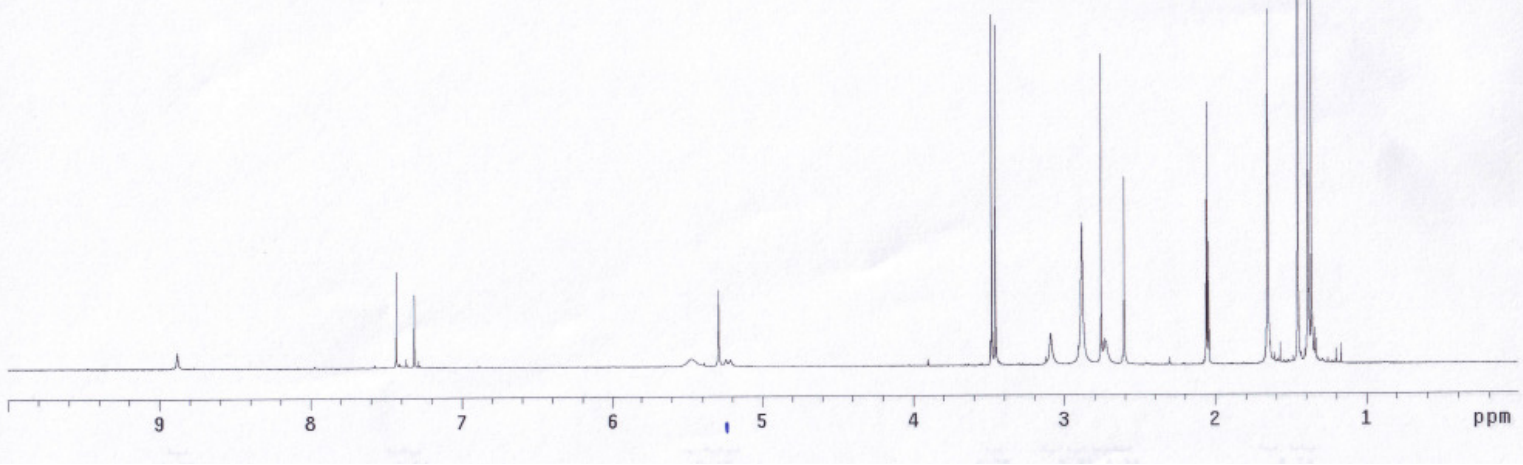
Pulse Sequence: s2pul

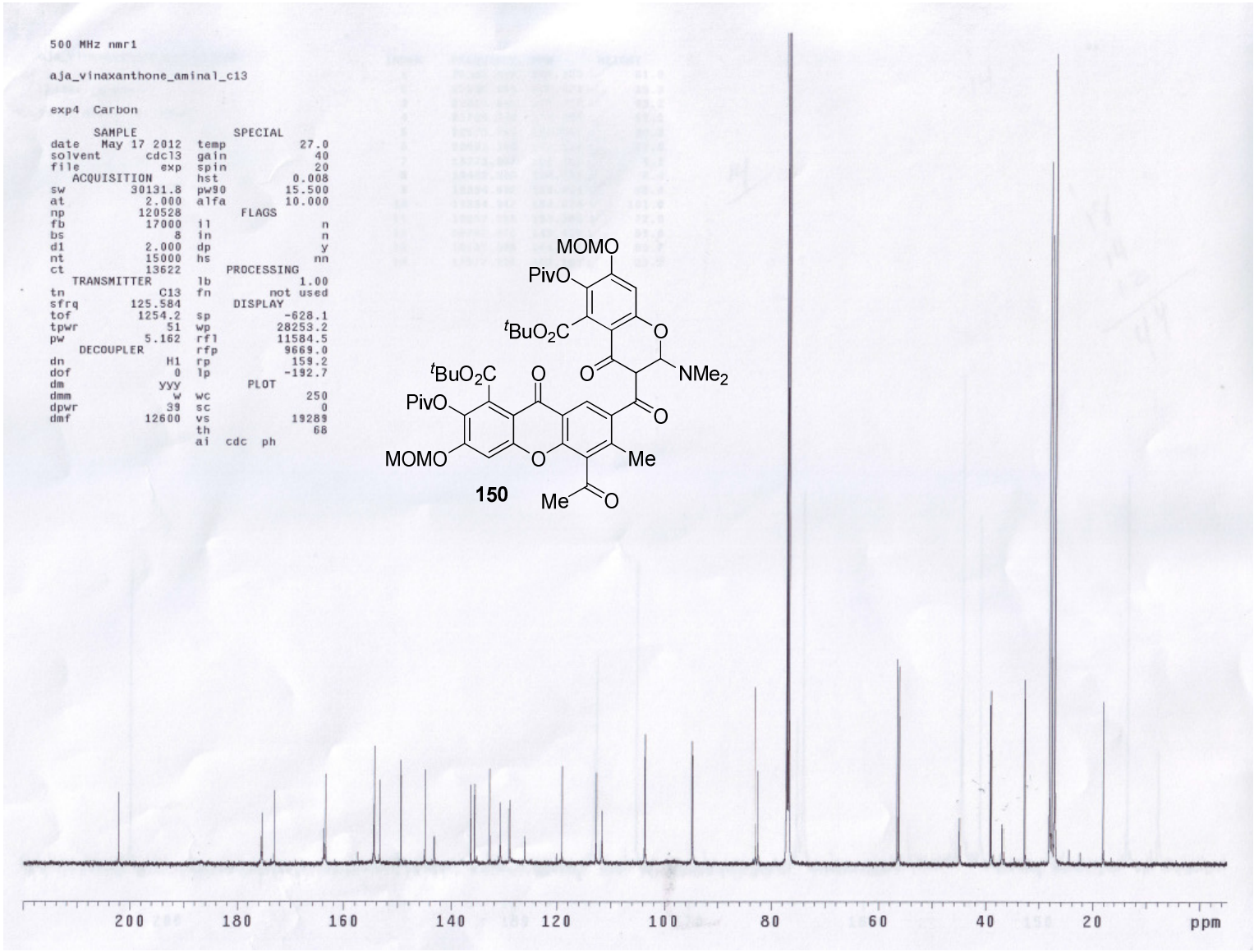
Solvent: acetone
Temp. 25.0 C / 298.1 K
File: PROTON_01
INOVA-500 "nmrfred"

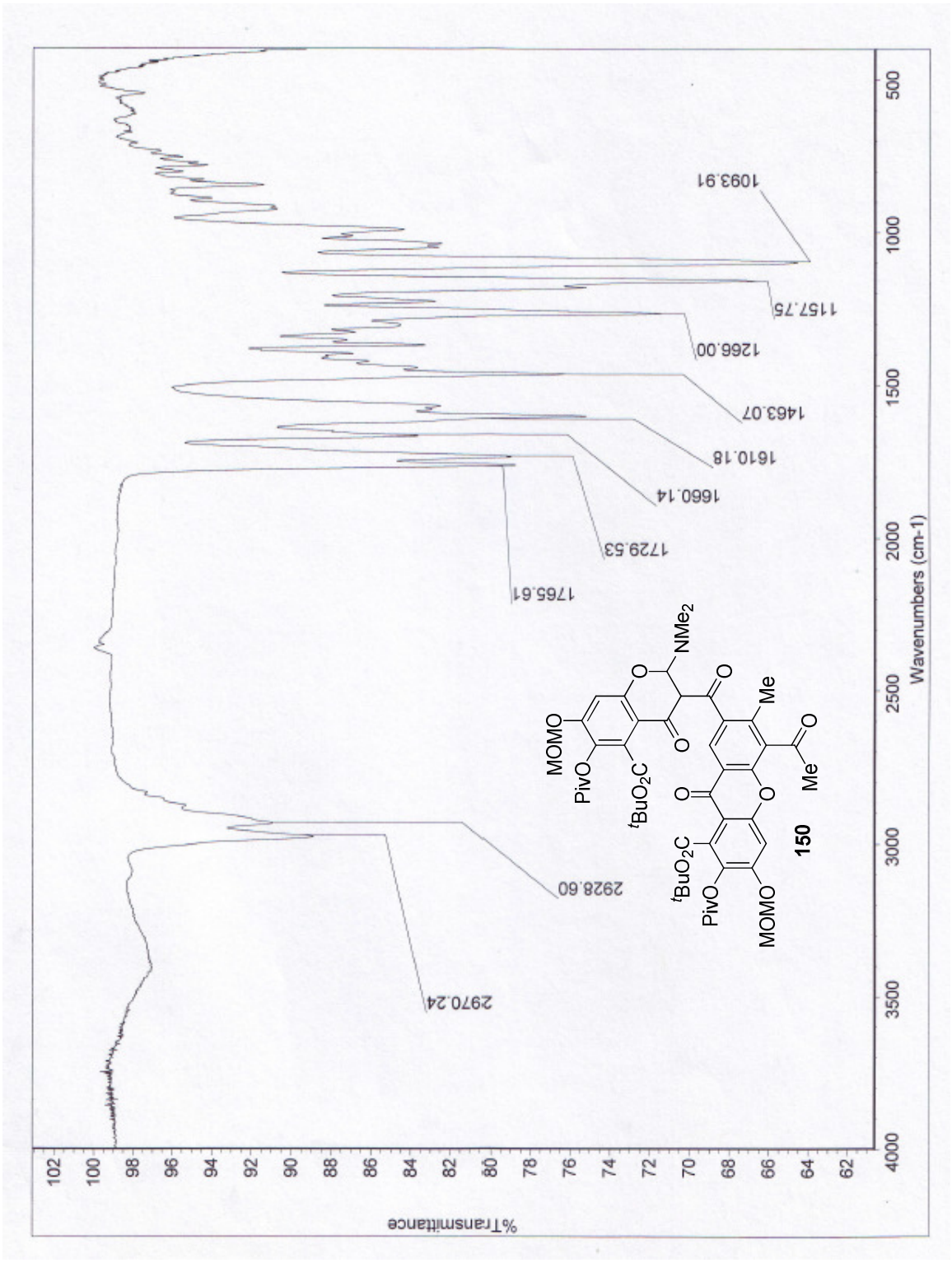
Relax. delay 1.000 sec
Pulse 45.0 degrees
Acq. time 2.556 sec
Width 6410.3 Hz
16 repetitions
OBSERVE H1, 399.6777962 MHz
DATA PROCESSING
FT size 32768
Total time 0 min, 57 sec

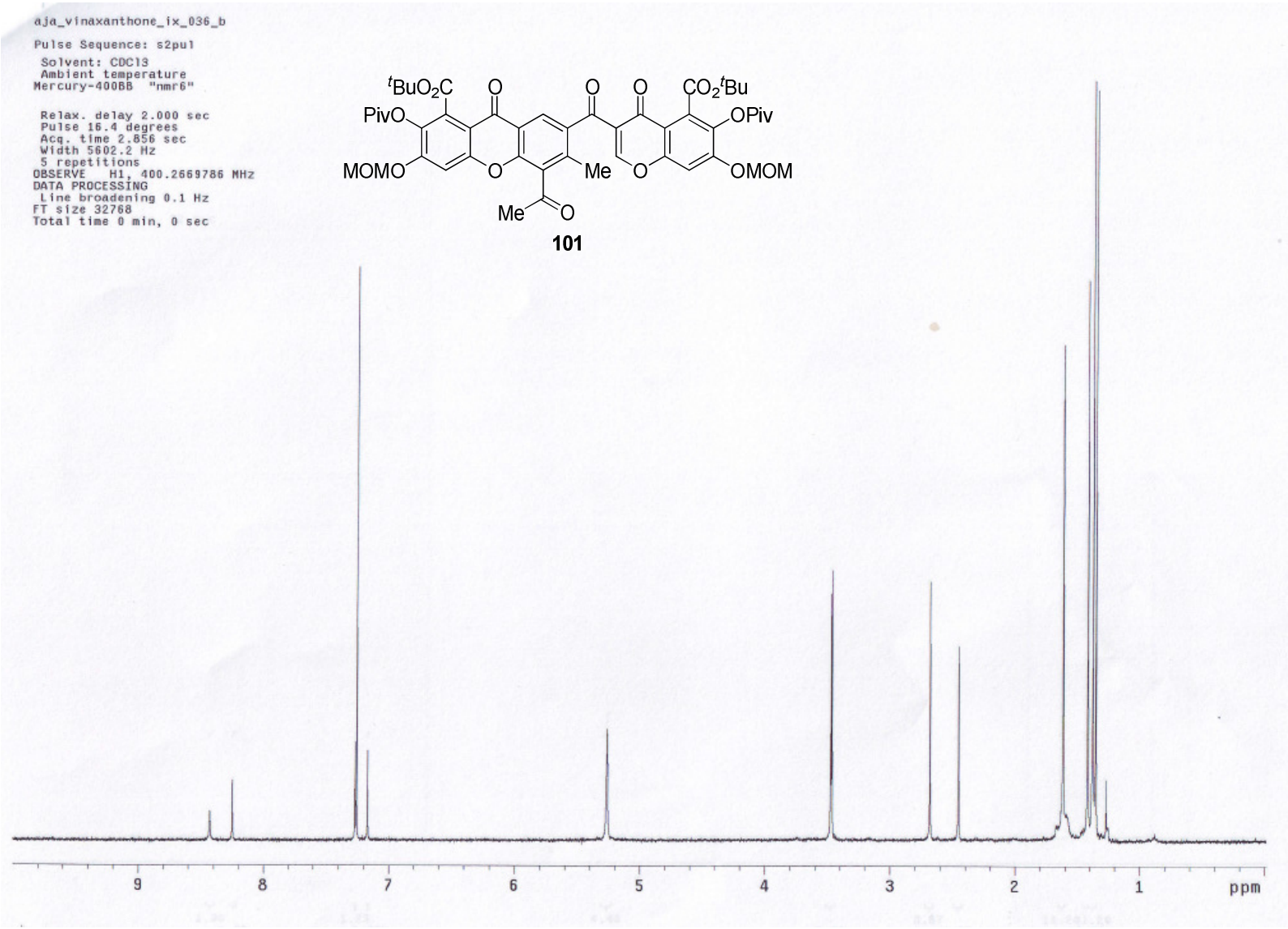


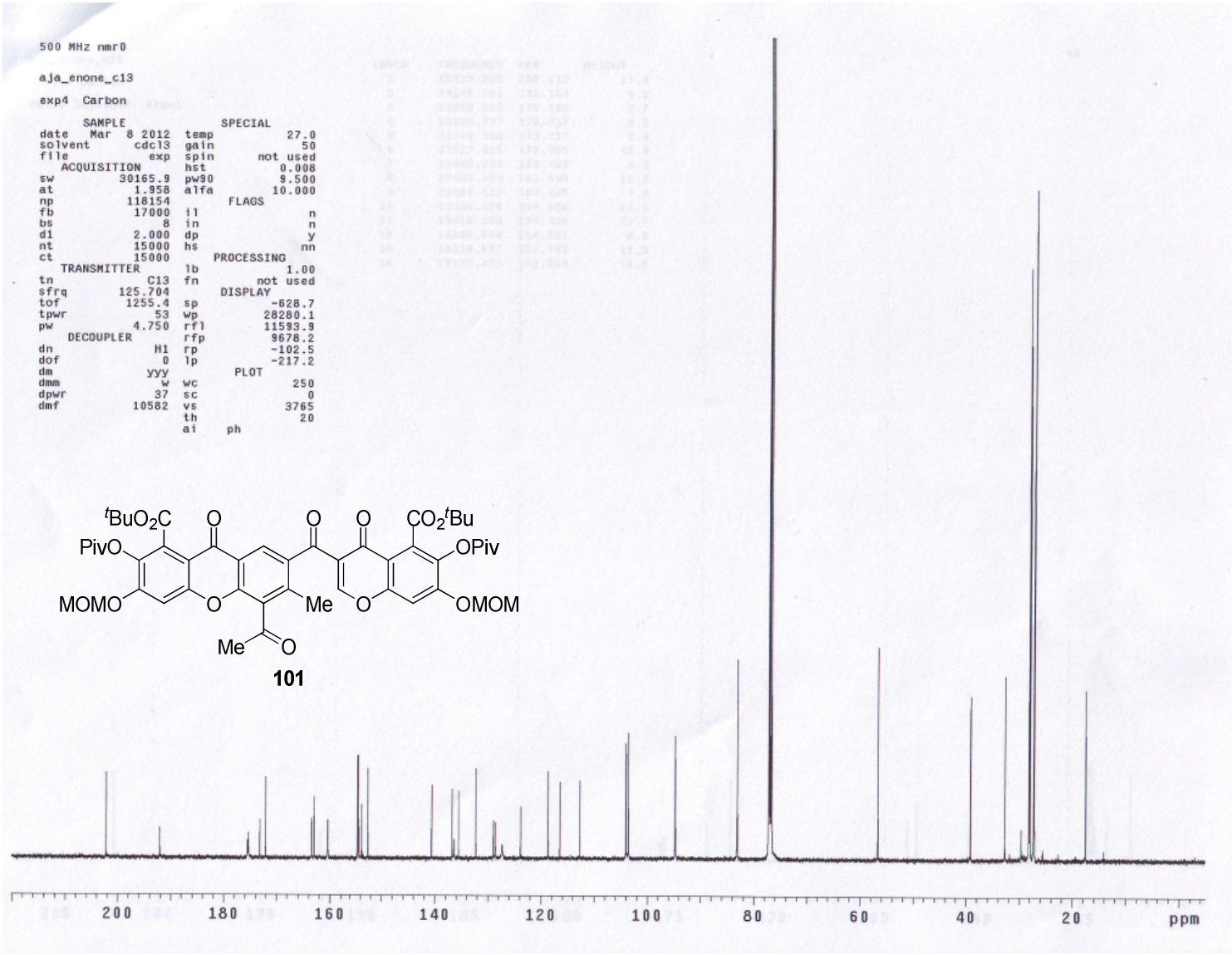
150

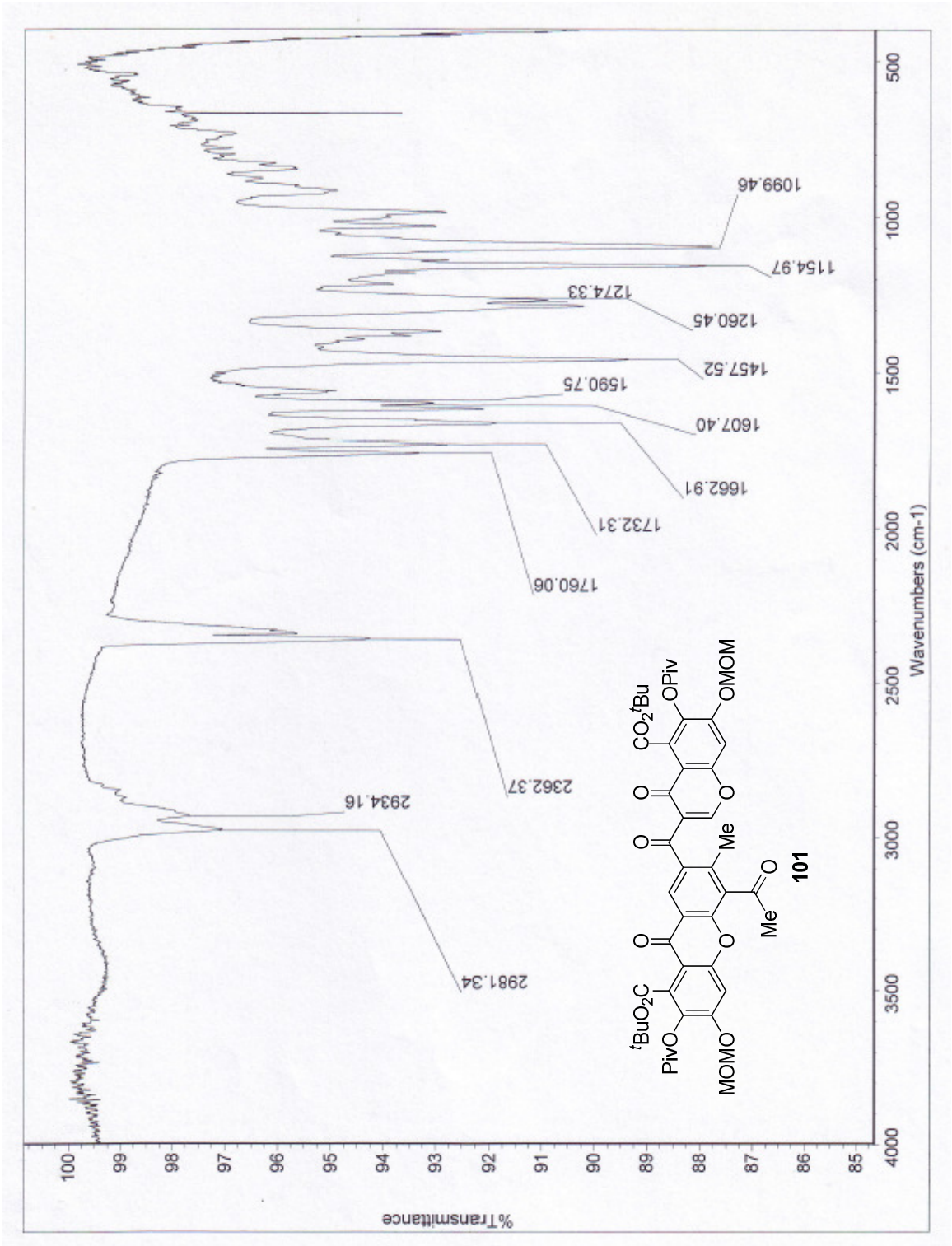


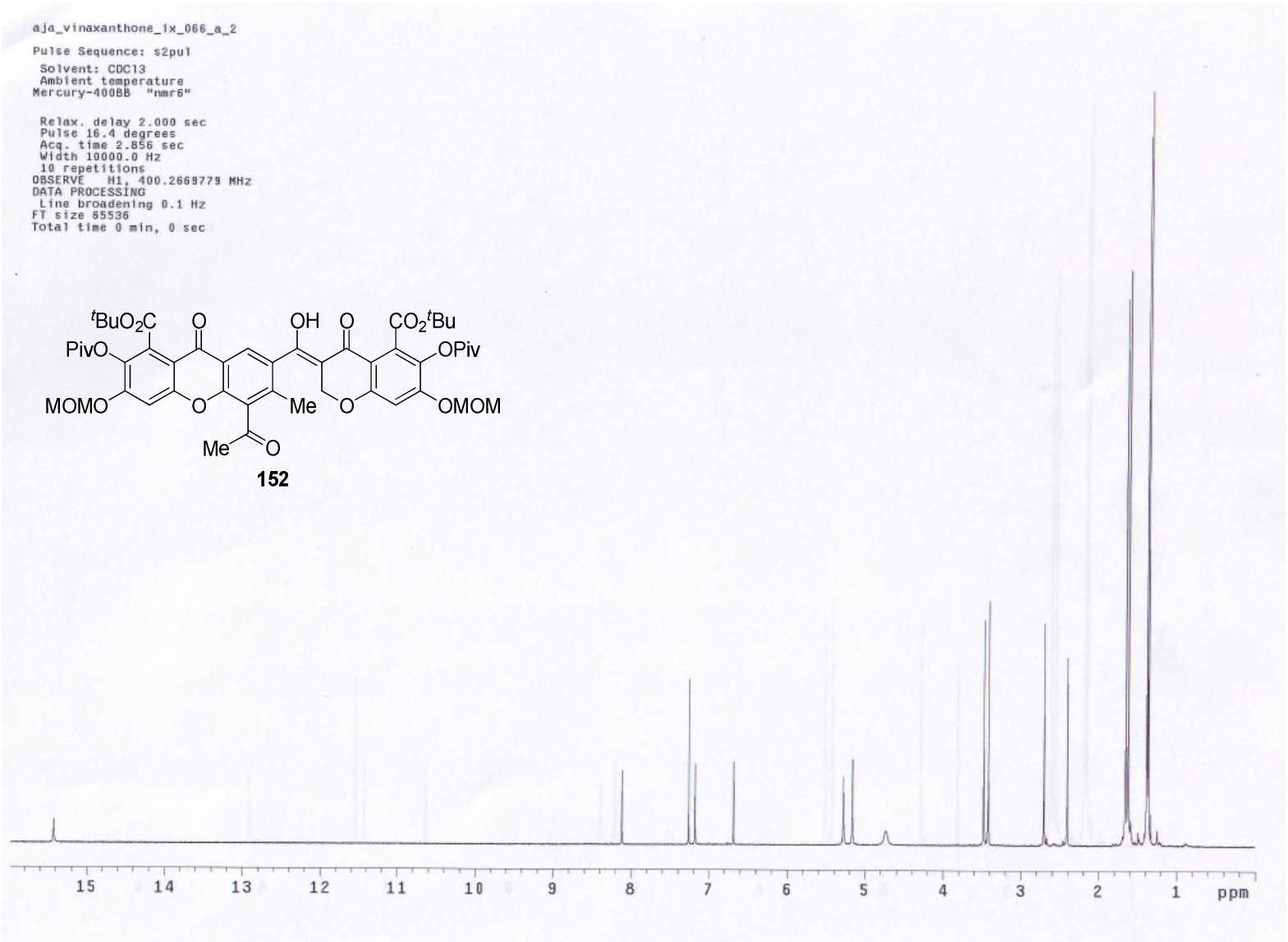

500 MHz nmr1
aja_vinaxanthone_aminal_c13
exp4 Carbon
SAMPLE
date May 17 2012
solvent cdcl3
file exp
ACQUISITION
sw 30131.8
at 2.000
np 120528
fb 17000
bs 8
d1 2.000
nt 15000
ct 13622
TRANSMITTER
tn C13
sfrq 125.584
tof 1254.2
tpwr 51
pw 5.162
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 39
dmf 12600
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 15.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.1
wp 28253.2
rfl 11584.5
rfp 9669.0
rp 159.2
lp -192.7
PLOT
wc 250
sc 0
vs 19289
th 68
ai cdc ph
MOMO
PivO
tBuO2C
O
NMe2
Me
150
200
180
160
140
120
100
80
60
40
20
ppm

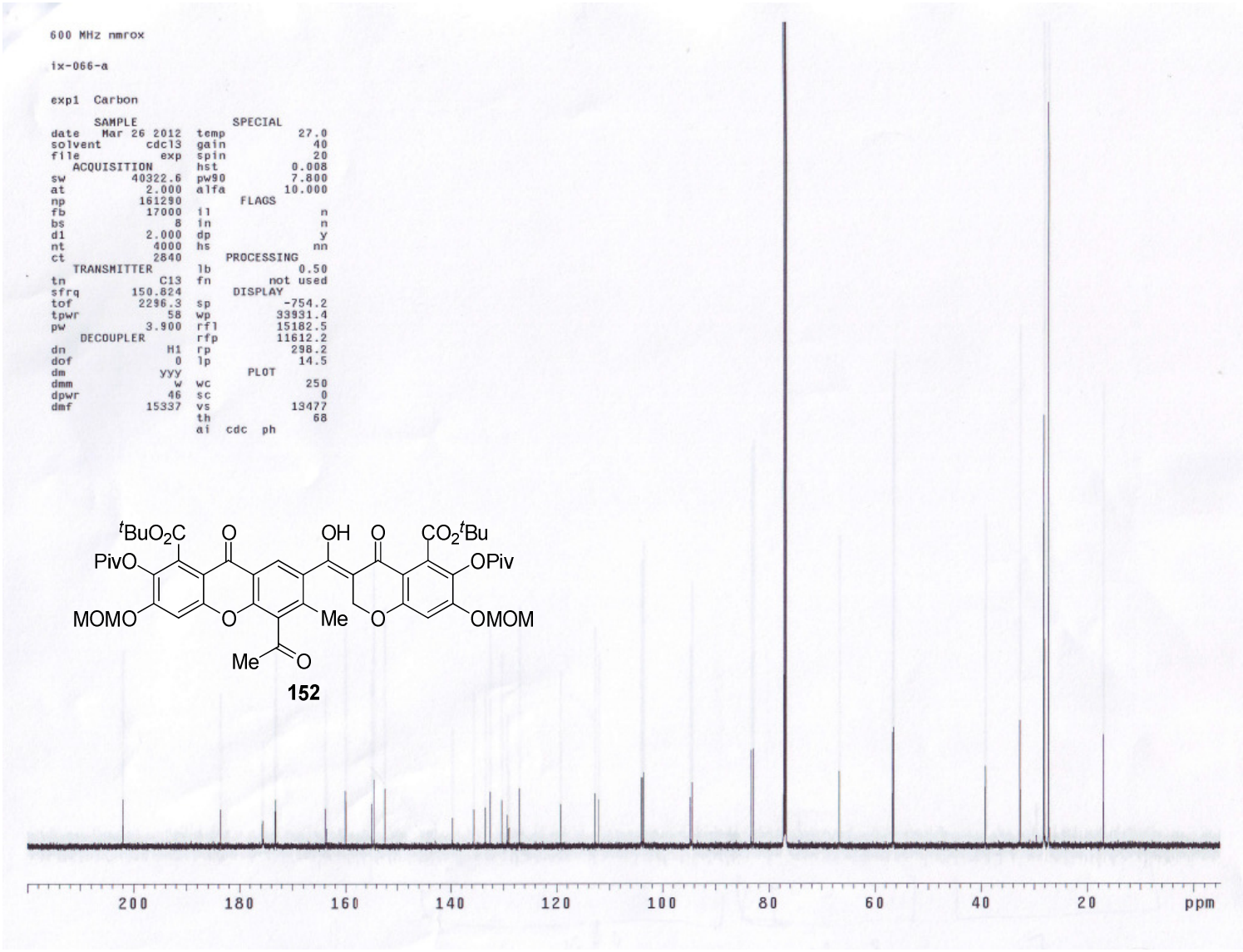

%Transmittance
Wavenumbers (cm-1)
2970.24
2928.60
1765.61
1729.53
1660.14
1610.18
1463.07
1266.00
1157.75
1093.91
MOMO
PivO
tBuO2C
NMe2
O
Me
Me
150

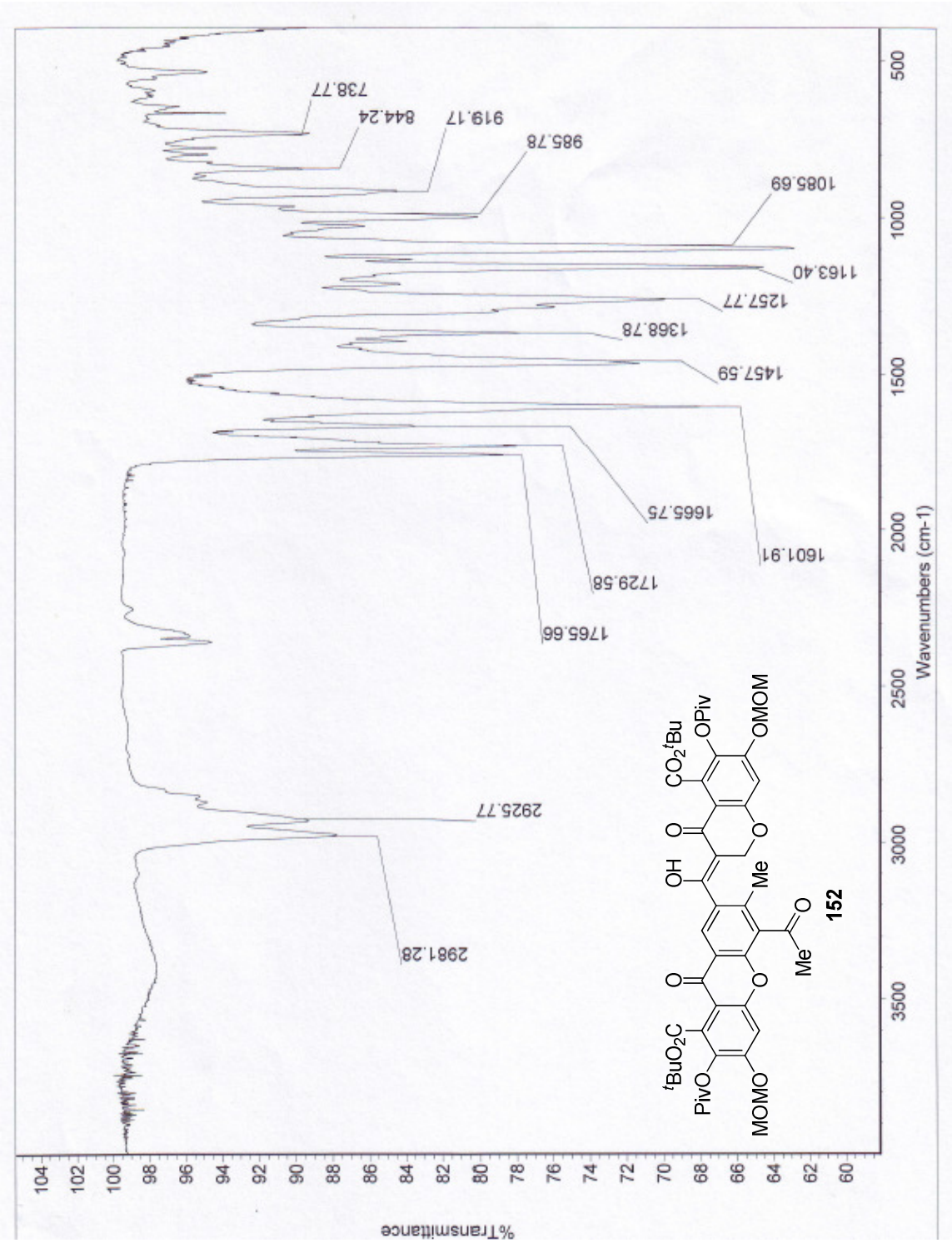

aja_vinaxanthone_ix_036_b
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 5602.2 Hz
5 repetitions
OBSERVE H1, 400.2669786 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 0 min, 0 sec
tBuO2C
CO2tBu
PivO
OPiv
MOMO
OMOM
Me
Me
101
9
8
7
6
5
4
3
2
1
ppm

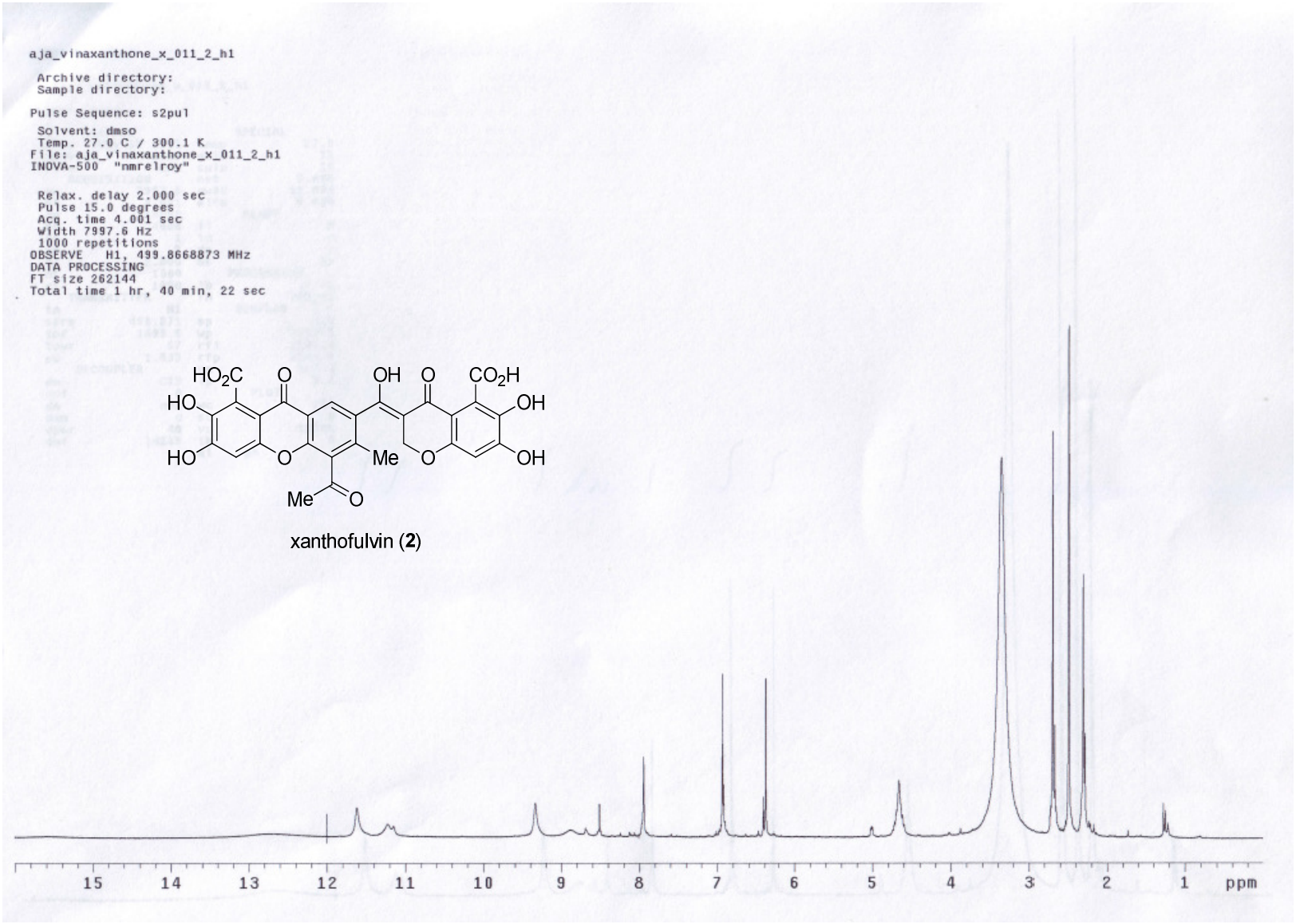

500 MHz nmr0
aja_enone_c13
exp4 Carbon
SAMPLE
date Mar 8 2012
solvent cdcl3
file exp
ACQUISITION
sw 30165.9
at 1.958
np 118154
fb 17000
bs 8
d1 2.000
nt 15000
ct 15000
TRANSMITTER
tn C13
sfrq 125.704
tof 1255.4
tpwr 53
pw 4.750
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 37
dmf 10582
SPECIAL
temp 27.0
gain 50
spin not used
hst 0.008
pw90 9.500
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 1.00
fn not used
DISPLAY
sp -628.7
wp 28280.1
rfl 11593.9
rfp 9678.2
rp -102.5
lp -217.2
PLOT
wc 250
sc 0
vs 3765
th 20
ai ph
tBuO2C
PivO
MOMO
O
O
O
O
CO2tBu
OPiv
Me
O
OMOM
Me
O
101
200
180
160
140
120
100
80
60
40
20
ppm


%Transmittance
Wavenumbers (cm-1)
2981.34
2934.16
2362.37
1760.06
1732.31
1662.91
1607.40
1590.75
1457.52
1260.45
1274.33
1154.97
1099.46
OMOM
OPiv
CO2tBu
MOMO
PivO
tBuO2C
Me
Me
101

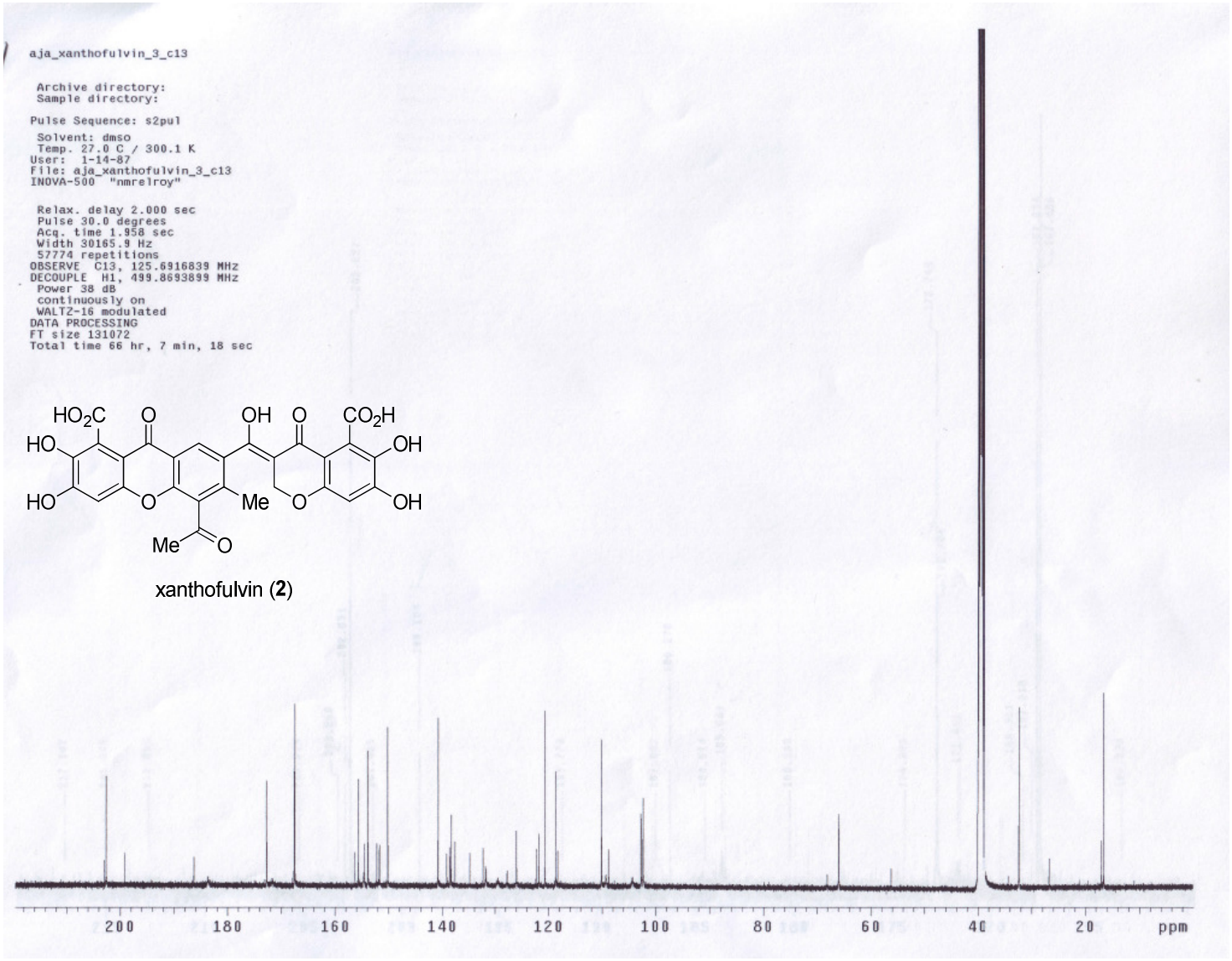

aja_vinaxanthone_ix_066_a_2
Pulse Sequence: s2pul
Solvent: CDCl3
Ambient temperature
Mercury-400BB "nmr6"
Relax. delay 2.000 sec
Pulse 16.4 degrees
Acq. time 2.856 sec
Width 10000.0 Hz
10 repetitions
OBSERVE H1, 400.2669779 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 0 min, 0 sec
tBuO2C
O
OH
O
CO2tBu
PivO
OPiv
MOMO
O
Me
O
OMOM
Me
O
152
15
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm


600 MHz nmrox
ix-066-a
exp1 Carbon
SAMPLE
date Mar 26 2012
solvent cdcl3
file exp
ACQUISITION
sw 40322.6
at 2.000
np 161290
fb 17000
bs 8
d1 2.000
nt 4000
ct 2840
TRANSMITTER
tn C13
sfrq 150.824
tof 2296.3
tpwr 58
pw 3.900
DECOUPLER
dn H1
dof 0
dm yyy
dmm w
dpwr 46
dmf 15337
SPECIAL
temp 27.0
gain 40
spin 20
hst 0.008
pw90 7.800
alfa 10.000
FLAGS
il n
in n
dp y
hs nn
PROCESSING
lb 0.50
fn not used
DISPLAY
sp -754.2
wp 33931.4
rfl 15182.5
rfp 11612.2
rp 298.2
lp 14.5
PLOT
wc 250
sc 0
vs 13477
th 68
ai cdc ph
tBuO2C
O
OH
O
CO2tBu
PivO
OPiv
MOMO
O
Me
O
OMOM
Me
O
152
200
180
160
140
120
100
80
60
40
20
ppm

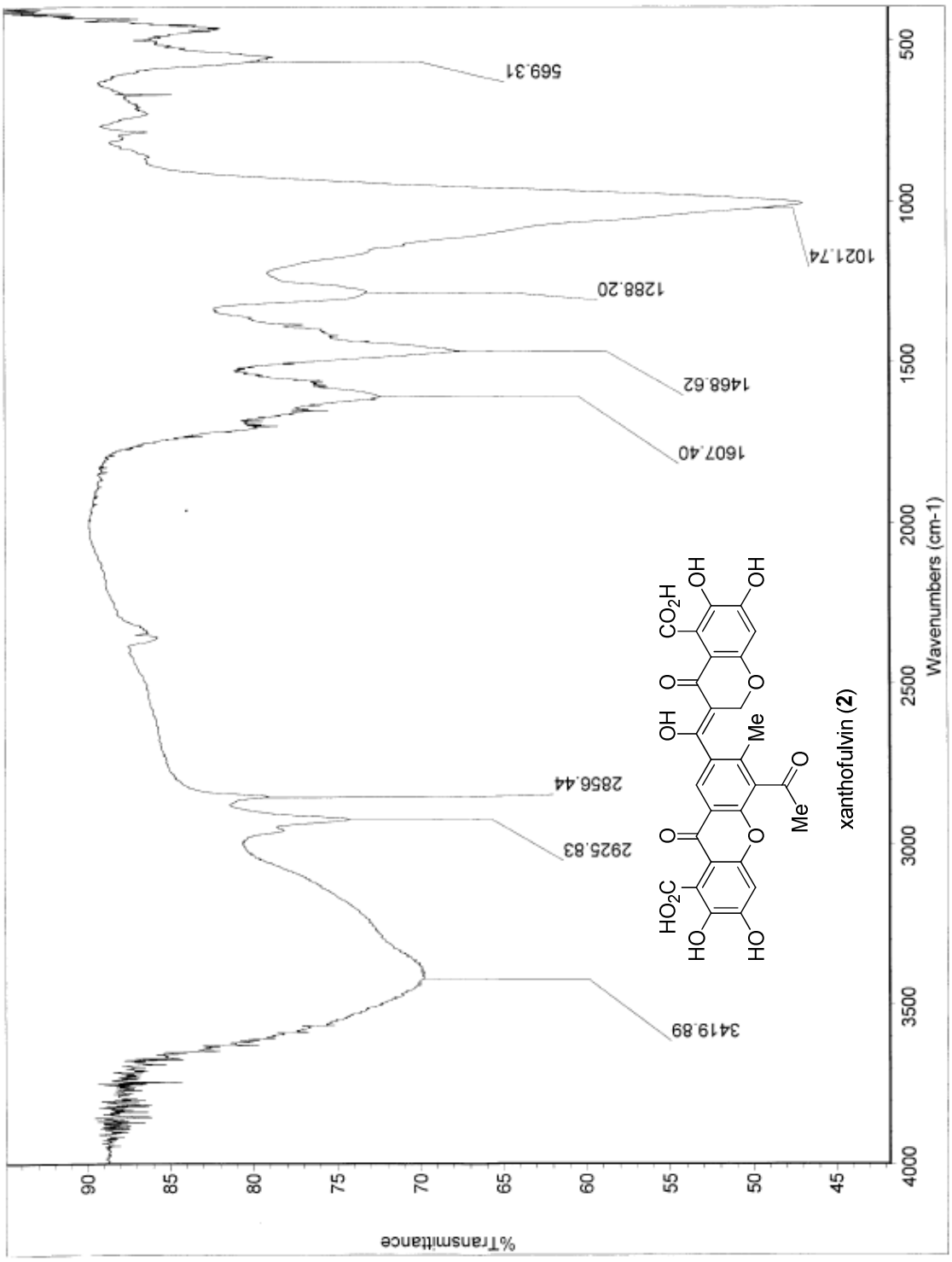

%Transmittance
Wavenumbers (cm-1)
2981.28
2925.77
1765.66
1729.58
1665.75
1601.91
1457.59
1368.78
1257.77
1163.40
1085.69
985.78
919.17
844.24
738.77
OMOM
OPiv
CO2tBu
OH
O
Me
Me
O
MOMO
PivO
tBuO2C
152



xanthofulvin (**2**)

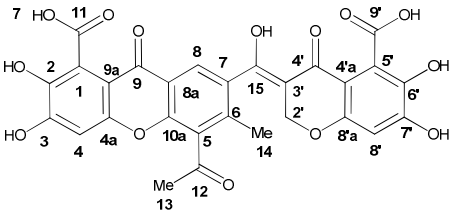


xanthofulvin (**2**)

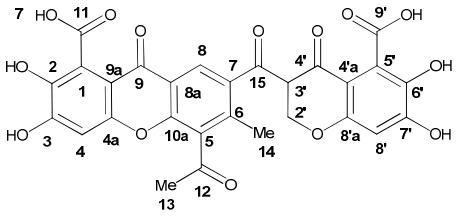

%Transmittance
Wavenumbers (cm-1)
3419.89
2925.83
2856.44
1607.40
1468.62
1288.20
1021.74
569.31
xanthofulvin (2)

Spectral Comparison.

Kumagai Numbering [22]



xanthofulvin (2)



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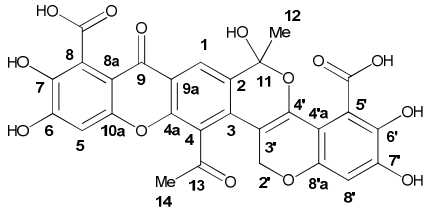
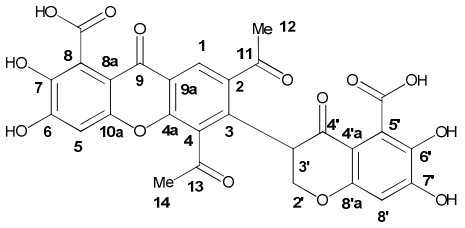
Wrigley 411J (Proposed) Numbering[1]



123



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Atom (Kumagai Numbering)	Siegel ^{13}C (Enol)	Siegel ^{13}C (Keto)	Kumagai ^{13}C (Enol)	Kumagai ^{13}C (Keto)	Atom (Wrigley Numbering)	Wrigley ^{13}C (Enol)	Wrigley ^{13}C (Keto)
12	202.6	202.9	202.7	202.9	13	202.4	202.5
4’	183.7	199.1	183.7	199.1	11	104.4	199.0
9	172.7	186.3	172.8	186.3	4	182.8	186.1
15	172.7	172.7	172.7	172.7	9	172.7	172.5
9’	167.5	167.7	167.5	167.6	5’-CO_2H	167.5	167.4
11	167.5	167.7	167.5	167.6	8-CO_2H	167.4	167.4
8’a	156.3	156.3	156.3	156.3	8’a	155.6	156.2
7’	154.5	154.7	154.5	154.5	7’	154.5	154.5
3	153.9	153.9	153.8	153.8	6	153.8	153.8
10a	152.2	152.2	152.2	152.2	4a	151.6	152.1
4a	150.2	150.1	150.2	150.1	10a	150.2	150.1
2	140.8	140.9	140.7	140.8	7	140.7	140.8
6	137.6	139.2	138.1	139.1	6’	138.6	137.5
6’	132.4	137.6	137.6	137.6	2	138.2	139.1
5	129.4	134.9	132.4	134.9	4	131.8	132.4
7	128.3	132.4	129.9	132.4	3	129.8	134.9
8	125.9	127.7	125.8	127.7	1	125.8	127.5
5’	120.7	122.2	120.6	122.2	5’	121.6	122.2
1	120.7	120.8	120.6	120.6	8	120.6	120.6

8a	118.7	118.3	118.5	118.2	9a	118.6	118.2
4'a	110.1	110.1	110.1	110.1	8a	110.0	110.1
9a	110.1	108.8	110.1	108.8	4'a	109.2	108.7
3'	104.4	56.3	104.2	56.2	8'	102.8	102.4
8'	102.4	102.4	102.3	102.3	5	102.3	102.3
4	102.4	102.4	102.3	102.3	2'	65.8	66.9
2'	65.9	56.3	65.7	56.2	3'	N/D	56.2
13	32.4	32.4	32.4	32.4	14	32.2	32.4
14	16.6	17.1	16.5	17.0	12	16.4	16.9

Atom (Kumagai Numbering)	Siegel ^{1}H (Enol)	Siegel ^{1}H (Keto)	Kumagai ^{1}H (Enol)	Kumagai ^{1}H (Keto)	Atom (Wrigley Numbering)	Wrigley ^{1}H (Enol)	Wrigley ^{1}H (Keto)

15-OH	15.61 (s, 1H)	N/D	N/D	N/D	N/D	N/D	N/D
11,9'-OH	12.75 (s, 2H)	N/D	12.71 (s, 2H)	N/D	8,5'-OH	N/D	N/D
2-OH	11.62 (s, 1H)	N/D	11.61 (s, 1H)	N/D	7-OH	N/D	N/D
6'-OH	11.23 (s, 1H)	11.15 (s, 1H)	11.22 (s, 1H)	N/D	6'-OH	N/D	N/D
3-OH	9.33 (s, 1H)	N/D	9.30 (s, 1H)	N/D	6-OH	N/D	N/D
7'-OH	8.69 (s, 1H)	8.88 (s, 1H)	8.70 (s, 1H)	N/D	7-OH	N/D	N/D
8	7.95 (s, 1H)	8.51 (s, 1H)	7.91 (s, 1H)	8.52 (s, 1H)	1	7.97 (s, 1H)	8.53 (s, 1H)
4	6.93 (s, 1H)	6.92 (s, 1H)	6.91 (s, 1H)	6.91 (s, 1H)	5	6.94 (s, 1H)	6.93 (s, 1H)
8'	6.39 (s, 1H)	6.42 (s, 1H)	6.40 (s, 1H)	6.40 (s, 1H)	8'	6.40 (s, 1H)	6.43 (s, 1H)
2'	4.66 (s, 2H)	5.01 (dd, J = 8.1, 4.7 Hz, 1H) 4.71	4.68 (s, 2H)	5.02 (dd, J = 11.6, 9.2 Hz, 1H) 4.71 (dd,	2'	4.69 (s, 2H)	5.04 (dd, J = 9.0, 5.0 Hz, 1H) 4.73

		(dd, *J* = 11.3, 4.2 Hz, 1H) 4.60 (m, 1H)		*J* = 11.6, 4.9 Hz, 1H) 4.61 (dd, *J* = 11.6, 9.2 Hz, 1H)			(dd, *J* = 11.0, 5.0 Hz, 1H) 4.64 (dd, *J* = 11.0, 9.0 Hz, 1H)
13	2.70 (s, 3H)	2.67 (s, 3H	2.69 (s, 3H)	2.67 (s, 3H)	14	2.71 (s, 3H)	2.68 (s, 3H)
14	2.31 (s, 3H)	2.29 (s, 3H)	2.28 (s, 3H)	2.28 (s, 3H)	12	2.33 (s, 3H)	2.31 (s, 3H)

Table 2. Spectral comparison for Siegel, Wrigley, and Kumagai.

References.

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